# 6 The Role for the DSB Response Pathway in Regulating Chromosome Translocations

Rajib Ghosh, Debamitra Das, and Sonia Franco

**Abstract**

In response to DNA double strand breaks (DSB), mammalian cells activate the DNA Damage Response (DDR), a network of factors that coordinate their detection, signaling and repair. Central to this network is the ATM kinase and its substrates at chromatin surrounding DSBs H2AX, MDC1 and 53BP1. In humans, germline inactivation of ATM causes Ataxia Telangiectasia (A-T), an autosomal recessive syndrome of increased proneness to hematological malignancies driven by clonal chromosomal translocations. Studies of cancers arising in A-T patients and in genetically engineered mouse models (GEMM) deficient for ATM and its substrates have revealed complex, multilayered roles for ATM in translocation suppression and identified functional redundancies between ATM and its substrates in this context. "Programmed" DSBs at antigen receptor loci in developing lymphocytes employ ubiquitous DDR factors for signaling and repair and have been particularly useful for mechanistic studies because they are region-specific and can be monitored *in vitro* and *in vivo*. In this context, murine thymocytes deficient for ATM recapitulate the molecular events that lead to transformation in T cells from A-T patients and provide a widely used model to study the mechanisms that suppress RAG recombinase-dependent translocations. Similarly, analyses of the fate of Activation induced Cytidine Deaminase (AID)-dependent DSBs during mature B cell Class Switch Recombination (CSR) have defined the genetic requirements for end-joining and translocation suppression in this setting. Moreover, a unique role for 53BP1 in the promotion of synapsis of distant DSBs has emerged from these studies.

**Keywords**

Class switch recombination · V(D)J recombination · AID · RAG · ATM · Chromosomal translocation

## 6.1 The DNA Damage Response (DDR) at Sites of Double-Strand Breaks (DSBs)

### 6.1.1 Overview: ATM Orchestrates the DDR in Mammalian Cells

DNA DSBs represent the most deleterious DNA lesion; failure to repair them may lead to genomic instability and cell death or senescence [45]. At

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the organismal level, defective DSB repair translates into tissue dysfunction and premature aging and promotes tumorigenesis [45]. To prevent these outcomes, mammalian cells have evolved the DDR, a rapid set of responses that coordinates the assembly of repair complexes at the break with the activation of cell cycle checkpoints and the transcriptional networks that ultimately mediate cellular outcomes [153]. Moreover, it is becoming apparent that the DDR is not limited to the nucleus but rather coordinates the nuclear and cytoplasmic responses to DNA damage [62].

This rapid and widespread response is made possible by coordinated posttranslational modifications of DNA repair factors and histones at the break site, including phosphorylation, ubiquitination, SUMOylation, PARylation and others [15, 16, 29, 85, 126, 127, 182, 192]. In the context of phosphorylation, the DDR is regulated by three highly related PI3 kinase-like kinases (PI3KKs): Ataxia Telangiectasia Mutated (ATM), Ataxia-telangiectasia and RAD3 Related protein (ATR) and the catalytic subunit of the DNA protein kinase (DNA-PKcs) [108]. All three factors are activated in response to DSBs and phosphorylate hundreds of substrates at target SQ/TQ motifs [112], often in a redundant manner [159, 174]. Their activity is regulated by multiple mechanisms, including the cell cycle [83] and their mutual interactions [119, 193] and ultimately promotes repair and suppresses chromosomal translocations. In this Chapter, we will focus on key roles for the ATM kinase and its substrates in translocation suppression. Please see Fig. 6.1 for introductory schematic of ATM domains and its main regulatory functions at sites of DSBs.

### 6.1.2 General Mechanisms of Translocation Suppression by the DDR

DSBs threaten genomic integrity because their repair may introduce mutations at the break site and/or proceed aberrantly to generate chromosomal rearrangements. Indeed, genome-wide mapping of chromosomal translocations arising in primary mouse B lymphocytes harboring traceable DSBs revealed that translocation formation is enhanced by proximity [44, 93], favoring intrachromosomal rearrangements and resulting in frequent deletions *in cis* [44, 93]. Although most of these translocations likely have no consequence to cellular functions, rare events may disable anti-cancer mechanisms via inactivation or overexpression of anti- or pro-oncogenic factors, respectively [64, 135]. Therefore, a key function of the DDR is to suppress pathogenic clonal translocations by promoting the rejoining of DNA ends across the break.

In mammalian cells, DSB rejoining is mediated via either Homologous Recombination (HR), an error-free pathway active in the replicative phases of the cell cycle [87, 134] or NonHomologous End-Joining (NHEJ), a versatile, ligase IV-dependent pathway that re-ligates broken DNA ends across the cell cycle using no homology or micro-homologies [21, 102]. In addition to the canonical NHEJ pathway, cancer cells may activate a back-up or alternative NHEJ pathway that rather employs ligase I/III and may repair persistent breaks with slower kinetics [41]. Regardless of the repair pathway used, DSB repair is slow (minutes to hours) and necessitates a strategy to prevent DNA end dissociation prior to ligation. This end tethering function is provided by the DDR in conjunction with repair factors. The complex formed by MRE11, RAD50 and NBS1 (MRN) ubiquitously binds to broken DNA ends and plays key roles in their sensing and processing throughout the cell cycle [164]. Specifically, the hook domains at the apex of two RAD50 coiled coil domains dimerize to bridge two DNA molecules bound by the RAD50 globular heads [78] and this function is facilitated by MRE11 dimerization [178]. Indirectly, the endonuclease activity of MRE11 initiates end-resection and activates the ATM kinase [129], a main orchestrator of the DDR [112]. This role for MRN in DNA end alignment and bridging is highly conserved and occurs in different chromatin contexts, including canonical and alternative NHEJ [50, 180] and programmed breaks generated during

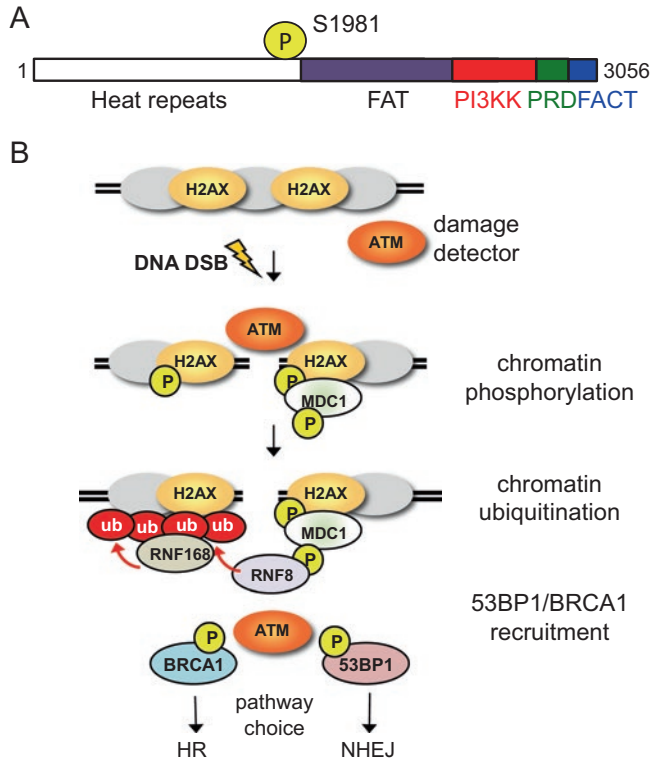


**Fig. 6.1** ATM is a kinase with pleiotropic roles in the DNA Damage Response (DDR). (**a**) The carboxi-terminal domain of ATM contains 40–50 alpha-helical repeats that mediate interaction with the MRE11/RAD50/NBS1 (MRN) complex. The carboxi-terminal domain contains a PI3 kinase-like kinase (PI3KK) domain that modifies S/T(Q) motifs in target proteins. The kinase domain is flanked by a FRAP-ATM-TRRAP (FAT) domain and a FAT carboxi-terminal (FACT) domain. ATM auto-phosphorylates at Ser1981 upon induction of double strand breaks (DSB) and the modified protein is commonly used as a biomarker for DDR activation. (**b**) ATM regulates the DDR at multiple steps, including the rapid detection of break-induced alterations in chromosomal structure leading to auto-phosphorylation at Ser1981 and activation; the maintenance of DNA end tethering via modification of MRE11/RAD50/NBS1 complex; the recruitment of ubiquitin ligases via phosphorylation of H2AX and MDC1; and the competition between 53BP1 and BRCA1 for DNA ends, a critical event during DSB repair pathway choice. ATM also phosphorylates many proteins in the nucleoplasm (such as p53) and outside the nucleus (no depicted)

V(D)J recombination [74] and Class Switch Recombination (CSR; see below) [54].

ATM, together with DNA-PKcs and ATR, phosphorylates the amino-terminal tail of histone H2AX at Ser139 to form γ-H2AX [142]. This modification spreads both sides of the break and anchors MDC1 [107] to form a platform for the recruitment of BRCA1, 53BP1 and their effectors [14]. These multiprotein complexes, detected as "foci" by standard immunocytochemistry assays, may themselves function as "glue" to suppress DNA end dissociation [11, 186, 191]. In addition to DDR factors, components of the NHEJ pathway have also been implicated in the formation of the synaptic complex via different mechanisms [28, 68, 157], and their absence eventually results in DNA end dissociation [30, 103]. Therefore, the DDR and the NHEJ pathway normally cooperate to maintain DNA ends aligned and tethered until ligated.

In addition to position, transcriptional status has emerged as a main determinant of translocation proneness. Indeed, unbiased genome-wide translocation sequencing in primary mouse cells

revealed that transcribed regions, and in particular active transcription start sites, are prone to translocations [44, 93]. Transcription results in the generation of R loops, short RNA-DNA hybrids that leave the nontemplate DNA strand exposed to mutagenic activities, such as oxidative stress, cellular cytidine deaminases or others [147]. R loops are abundant in human cells [65] and, in some contexts, have been clearly shown to promote DNA DSBs and chromosomal translocations [76, 82]. The best characterized example is perhaps the promotion of chromosomal translocations between C-MYC and the immunoglobulin heavy chain (IgH) locus, a hallmark of many B cell malignancies [140]. R loops form at the at the MYC locus [59] and at the S region of the immunoglobulin heavy chain [23, 188]. AID, a cytidine deaminase expressed in B cells, binds to and modifies these structures, leading to formation of DNA DSBs and IgH-MYC translocations [59]. In support of a mechanistic role for R loops in this setting, loss of TOP3B, which relaxes negative supercoiling and increases R loop formation at the MYC promoter, also increases the frequency of Igh-Myc translocations in mice [183]. Moreover, AID induces translocations involving a heterologous S region and MYC in yeast THO mutants, known to accumulate R loops [144]. Together, these data suggest that the simultaneous formation of R loops in Ig and transcribed MYC (or other transcribed genes) may promote their translocations. Recent evidence indicates that many DDR and DNA repair factors may suppress chromosomal translocations via direct modulation of R loop formation and dissolution ([20, 73]; reviewed in [162]). In this context, ATM, a suppressor of IgH-Myc translocations *in vivo* [135], also suppresses R loop formation in proliferating cells [184] and is activated by R loops at sites of UV-induced DNA damage [169]. Finally, emerging data implicates transcription-independent DSBs generated by topoisomerase 2B (TOP2B) at chromosome loop anchors as a cause of chromosomal fragility [36], another scenario where the DDR may function to limit translocations.

## 6.2 Mammalian Genetic Models to Study Roles for the DDR in Translocation Suppression

### 6.2.1 Genetically Engineered Mouse Models (GEMM) of DDR Deficiency

Mice with germline inactivation of DDR factors have provided valuable insights into their requirements in translocation suppression. Embryonic fibroblasts and B and T lymphocytes deficient for ATM [34, 64], histone H2AX [12, 40, 64], MDC1 [107] or 53BP1 [64, 117] all accumulate chromosomal translocations. Mechanistically, these translocations are though to occur as a result of defective end-joining across the break leading to persistent breaks and end dissociation [11, 63]. In addition, DDR factors may play roles in the regulation of pathway choice during translocation. For example, ATM and H2AX not only suppress translocations but also enhance fidelity at translocation breakpoints by promoting rejoining via classical over alternative NHEJ [19]. Although all H2AX [31], MDC1 [81, 96, 109, 110] and 53BP1 [42, 61] are ATM substrates in the DDR, their roles in translocation suppression are not fully epistatic with ATM. In this regard, cytogenetic analysis of primary B and T cells deficient for 53BP1 and ATM revealed increased frequency of chromosomal breaks and translocations in double mutant primary cells associated to a greater defect in end-joining [146]. Similarly, combined deficiency for H2AX and ATM leads to a marked increase in the frequency of chromosomal breaks and translocations in embryonic fibroblasts [190] and *in vitro* cultured T cells [185]. However, mechanistic understanding of these interactions has mostly relied on the analysis of translocations arising at loci undergoing programmed DSBs during lymphocyte development, which can be traced in time and space. In Section 3 below, we discuss roles for ATM and its substrates in translocation suppression using RAG-dependent DSBs during V(D)J recombination as a model system. Furthermore, Section 4

summarizes our understanding on how the ATM network suppresses AID-dependent translocations during Class Switch Recombination (CSR).

### 6.2.2 Human Genetic Syndromes of DDR Deficiency: Ataxia-Telangiectasia

Mutations in H2AX, MDC1 or 53BP1 have not been observed in humans. In contrast, biallelic mutations in the ATM kinase result in the autosomal recessive syndrome Ataxia-Telangiectasia (A-T; OMIM#208900). The ATM locus at human chromosome 11q22 contains 66 exons and encodes a 350 kDa protein with a C-terminal PI3 kinase-like kinase (PI3KK) domain [149]. Mutations leading to A-T span the entire locus and most patients are compound heterozygous [167]. Approximately 85% of A-T patients harbor biallelic null mutations and display the most severe or "classical" form of the disease, including neurodegeneration, immunodeficiency and increased cancer predisposition [22, 143]. Neurodegeneration is particularly severe in the cerebellum, with progressive loss of Purkinje cells (PC) and, to a lesser extent, granule cells (GCs) [25, 128, 173]. On average, ataxia first manifests in the toddler years and patients become wheelchair bound at a mean age of 8 years [120]. Currently, the mechanisms leading to neurodegeneration remain unclear. In contrast, the phenotypes of immunodeficiency, gonadal atrophy, radiosensitivity, premature aging and cancer proneness are clearly related to ATM functions in DSB repair. In this regard, A-T primary cells show frequent chromosomal breaks and translocations [94, 95]. Moreover, accelerated telomere shortening [114, 125, 155, 170, 179], defective response to oxidative stress [70] and other phenotypes may cooperate with defective DSB repair to augment genomic instability in A-T cells. Lymphocytes from A-T patients harbor chromosomal breaks and clonal translocations that mainly involve T [77, 92, 94] and B [32] cell receptor loci. These translocation are detected in the blood of many A-T patients years prior to the development of malignancy [165] and are discussed in detail in below.

## 6.3 The DDR Suppresses Chromosomal Translocations During V(D)J Recombination

### 6.3.1 Mechanisms of V(D)J Recombination

Adaptive immunity relies on the clonal expansion of B and T lymphocytes upon binding of their surface receptors to specific antigens [48, 168]. The generation of both B and T cells involves the expression of the lymphocyte-specific RAG1/RAG2 (RAG) endonuclease to introduce DSBs between V, D and J coding sequences and their flanking recombination signal sequences (RSS) at antigen receptor loci, followed by deletional or inversional recombination [151]. To prevent genomic instability, this process is initiated and completed during the G1 phase of the cell cycle [88, 152]. In the bone marrow, B lineage cells successively rearrange their V to D gene segments in the variable region of the immunoglobulin heavy chain (IgH) and light chain (IgL) loci to form pre-B cells [106]. Additional rearrangement of D to J gene segments yields mature B cells that express the B cell receptor (BCR) and exit the bone marrow to colonize the spleen and lymph nodes [106] (diagrammed in Fig. 6.2). Similarly, developing T cells in the thymus sequentially rearrange V, D and J gene segments to generate T cell receptors TCRα, TCRβ, TCRγ and TCRδ. TCRβ, TCRγ and TCRδ variable region exons are assembled first, at the $CD4^-/CD8^-$ ("double negative") stage. Productive VδDδJδ and VγJγ rearrangements generate TCRδ and TCRγ chains, respectively, which assemble in the surface to form the TCRγδ receptor and induce differentiation along this lineage [18]. Alternatively, a productive VβDβJβ rearrangement generates TCRβ chains that promote differentiation to the $CD4^+/CD8^+$ ("double positive") stage. Here, a productive VαJα rearrangement generates a TCRα chain that associates with TCRβ to promote differentiation to either $CD4^+$ or $CD8^+$ ("single positive") T cells [18].

In all cases, successful recombination requires the rejoining of RAG-liberated DSBs via ubiquitous DDR and NHEJ factors [10, 104]. Therefore, deficiencies for RAG as well as many DDR/NHEJ factors block B and T cell develop-

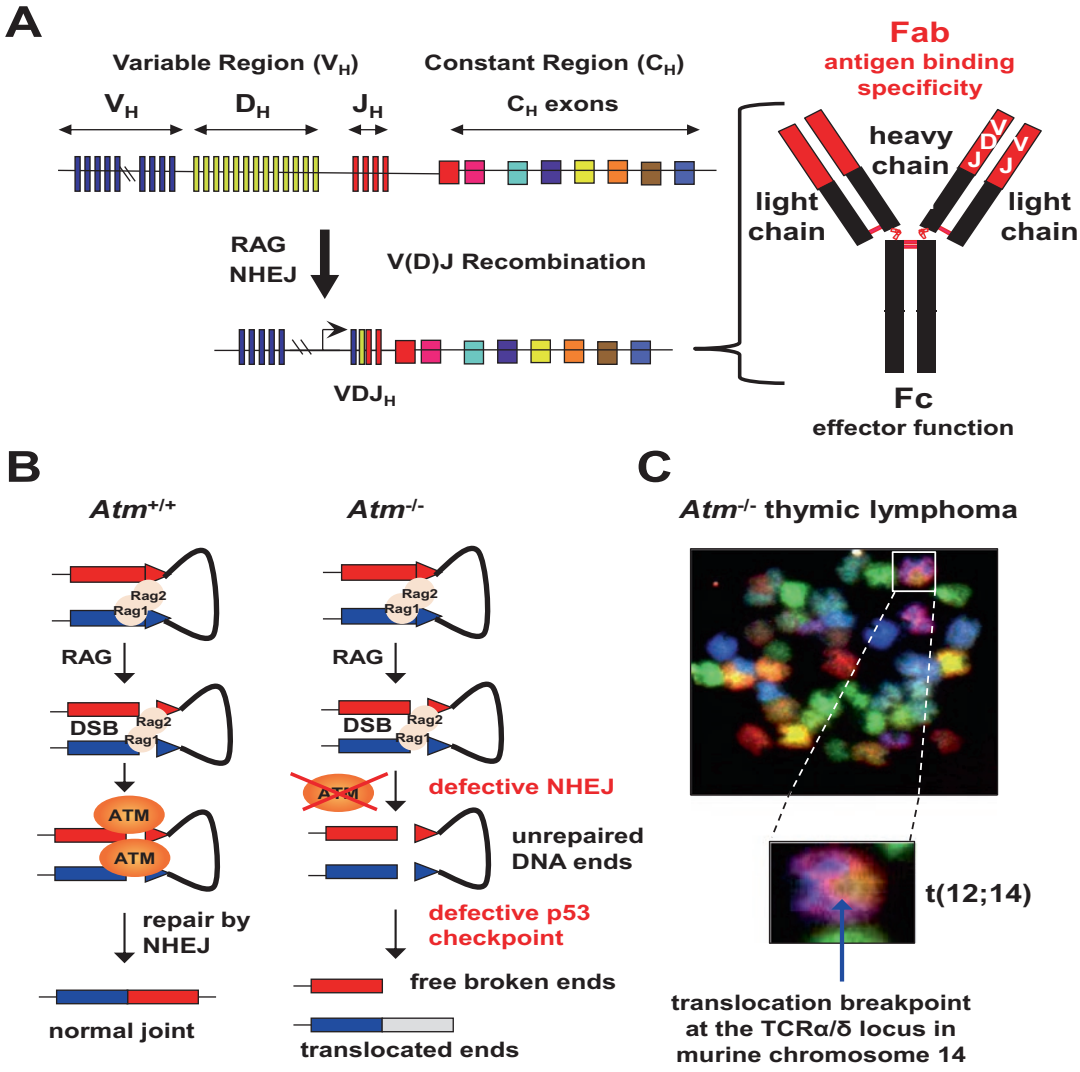


**Fig. 6.2** The DDR prevents translocations of RAG-dependent DSBs. (**a**) Schematic of the immunoglobulin heavy chain (IgH) locus at mouse chromosome 12. During V(D)J recombination, the RAG recombinase introduces double-strand breaks (DSBs) adjacent to $V_H$, $D_H$ and $J_H$ segments and the Nonhomologous End-Joining (NHEJ) pathway of DSB repair ligates the ends to generate a coding $VDJ_H$ exon. The expression of this $VDJ_H$ exon and a downstream constant region ($C_H$) exon generates the immunoglobulin heavy chain (IgH). The immunoglobulin light chain (IgL) is similarly generated via $V_L$ to $J_L$ recombination at the immunoglobulin light chain kappa (Igκ) or lambda (Igλ) loci. Binding of heavy and light chains results in antibody formation (depicted on the right). (**b**) Schematic of molecular events at the TCRα/δ locus in developing murine thymocytes. In wild-type mice (*Atm*$^{+/+}$ mice), RAG-dependent DSBs are sensed and signaled by ATM and repaired via NHEJ. In mice with a germline deletion of Atm (*Atm*$^{-/-}$ mice), a subset of RAG-dependent DSBs dissociates prior to repair, leading to either free, unrepaired DNA ends or aberrant repair by translocation to another broken DNA ends elsewhere in the genome. (**c**) Spectral karyotyping (SKY) analysis of thymic lymphomas arising in *Atm*$^{-/-}$ mice reveals a clonal translocation involving chromosomes 12 and 14. The breakpoint at chromosome 14 localizes to the TCRα/δ locus

ment at early stages to variable extent [156]. Specifically, loss of RAG results in a complete block or severe combined immunodeficiency (scid) with antigen receptor loci in germline configuration. In contrast, loss of DDR or NHEJ factors results in variable degrees of

immunodeficiency as a result of failed recombination of RAG-dependent DSBs. It is only in the latter scenario that unrepaired DSBs signal cell death or engage in chromosomal translocations. Moreover, concomitant defects in DSB repair elsewhere often lead to coexisting nonimmunological manifestations.

In mice and humans, the genes encoding TCRα and TCRδ occupy the same locus in chromosome 14 and their sequential rearrangement is regulated via specific enhancers [98]. Both human and mouse TCRδ loci resided between Vα and Jα segments, and therefore TCRα rearrangement deletes the TCR δ gene and commits cells to the α/β lineage. These rearrangements are driven by specific enhancer elements, Eδ and Eα [154], which play major roles in the generation of translocations (see below).

### 6.3.2 RAG-Dependent Breaks and Translocations in DDR-Deficient Mice

Recombining thymocytes deficient for NHEJ factors (including Ku70, Ku80, DNA-PKcs, Artemis, ligase IV or XRCC4) fail to ligate RAG-generated DSBs, leading to pro-B and pro-T cell apoptosis and absence or marked depletion of mature lymphocytes [3]. In contrast, deficiencies for DDR factors result in variable, milder defects in T cell maturation, in line with their redundant roles in DSB detection and signaling. Deficiency for components of the MRN complex [74] or ATM [7] results in the most severe defects, while residual recombination and lymphocyte development is observed in thymocytes deficient for ATM substrates H2AX [13, 40], MDC1 [107] or 53BP1 [176]. Of note, deficiencies for specific factors impact B and T cell development to different extent. For example, loss of ATM results in marked depletion of thymocytes and peripheral T cells early in life, while the B cell compartment is less affected.

*Atm*$^{-/-}$ mice [7, 24, 181, 190] have been particularly valuable to understand how the DDR suppresses the translocation of RAG-induced DSBs during in developing lymphocytes (Fig. 6.2). Cytogenetic analysis of interphase and dividing *Atm*$^{-/-}$ thymocytes and peripheral T cells has been used extensively to quantify chromosomal breaks at the TCRα/δ locus [24, 80, 105]. Moreover, this approach also allows monitoring of their progression to nonclonal chromosomal translocations and, over a period of a few months, clonal selection and full malignant transformation [7, 24, 181, 190]. The rapid clonal progression uniquely observed in this model results from the requirement for ATM in the activation of the p53-dependent G1/S cell cycle checkpoint [37, 91] and apoptosis in response to unrepaired DSBs [58]. Thus, rapid transformation observed in thymocytes deficient for ATM but not its substrates (see below) results from the unique pleomorphic roles for ATM in DSB detection, signaling and repair [34]. Interestingly, breeding into a RAG-deficient background does not prevent lymphomagenesis in *Atm*$^{-/-}$ mice [132, 133]. However, lymphomas in *Atm*$^{-/-}$/*Rag2*$^{-/-}$ mice lack chromosomal translocations involving antigen receptor loci [132, 133], further highlighting the essential role for ATM in promoting repair in this context. Finally, we note that ATM is activated in response cellular stresses other than DSBs [129], a mechanism that may potentially cross-talk with its functions at the DDR to modulate the fate of RAG-dependent DSBs .

*Atm*$^{-/-}$ thymi show blockade at the DP to SP transition and marked reductions in total cellularity, α/β T cells and SP CD4$^{+}$ and CD8$^{+}$ T cells [7, 24, 181, 190]. Consistent with defective repair of RAG-induced DSBs in the absence of ATM, fluorescence in situ hybridization (FISH) analyses of *Atm*$^{-/-}$ T cells with probes that hybridize to sequences flanking the TCRα/δ locus in chromosome 14 reveal frequent locus-specific chromosomal breaks [34, 105] (see Fig. 6.2 for an example).

*Atm*$^{-/-}$ mice succumb to T-cell acute ALLs with clonal translocations that typically involve the TCRα/δ locus in chromosome 14, the TCRβ locus on chromosome 6 and the immunoglobulin heavy chain locus in chromosome 12 that recombines D and J segments in thymocytes [33, 105, 189]. Moreover, T cells harboring translocations with a breakpoint at this locus are detected in the

peripheral blood of *Atm*$^{-/-}$ mice [34, 105], harboring the onset of malignancy. Mechanistically, elegant experiments by Sleckman and colleagues demonstrated that ATM functions to maintain RAG-generated DNA ends in repair complexes [26], preventing DNA end dissociation and chromosomal translocation.

Using array comparative genomic hybridization (CGH) analysis to map the translocation breakpoints within TCRα/δ, Zha and colleagues demonstrated that the TCRα/δ translocation is associated to defective rearrangement at the TCRδ rather than the TCRα locus [189], suggesting an earlier developmental origin than previously thought [33]. In support of this notion, deletion of Eδ [89] but not Eα [189] rescued clonal translocations *in vivo*. In addition, the CGH data revealed that the T(12;14) is associated to amplification of a set of genes upstream of the TCRα/δ locus [189], suggesting that breakage-fusion-bridge (BFB) cycles may act as intermediaries. Todate, it remains unclear whether the sequences in chromosome 12 represent "passengers" or, alternatively, contribute to tumorigenesis by inactivating a tumor suppressor gene [189]. In this regard, the translocation deletes one copy of Bcl11b [189], a haploinsufficient tumor suppressor in the mouse [90], leading to decreased expression [189]. However, monoallelic deletion of Bcl11b in double negative thymocytes did not accelerate lymphomagenesis in *Atm*$^{-/-}$ mice [60], suggesting an alternative mechanism. Finally, the murine translocation deletes TCL1 [189], a gene that is translocated in the human translocation, even though it is located in the syntenic area.

ATM substrates H2AX, MDC1 and 53BP1 have also been implicated in the suppression of chromosomal translocations in developing lymphocytes. Immuno-FISH using antibodies that recognize γ-H2AX and DNA probes that hybridize to sequences at TCR loci revealed the presence of γ-H2AX foci at chromatin surrounding RAG-dependent DSBs [43]. The functional significance of this ATM- (and likely DNA-PKcs-) dependent modification has been investigated in detail using mice with germline [13, 40] or T cell-specific [185] H2AX inactivation. Collectively, these studies clearly demonstrate a requirement for H2AX for end-joining of RAG-dependent DNA ends at the TCRα/δ locus via its functions in DNA end anchoring prior to ligation [11, 186] and in protection from aberrant CtIP-mediated resection [75].

Interestingly, the presence of persistent, unrepaired RAG-dependent breaks in *H2afx*$^{-/-}$ thymocytes is not sufficient to trigger transformation and *H2afx*$^{-/-}$ mice are not lymphoma prone [13, 40]. This is likely due to the vigorous p53-dependent apoptotic response elicited by DSBs in *H2afx*$^{-/-}$ developing T cells. Indeed, breeding of *H2afx*$^{-/-}$ mice to mice with germline inactivation of p53 (*Trp53*$^{-/-}$ mice), themselves lymphoma prone [55, 72, 84], greatly accelerates lymphomagenesis relative to single mutants [13, 39]. Most significantly, the mechanisms driving transformation in *Trp53*$^{-/-}$ and *H2afx*$^{-/-}$/ *Trp53*$^{-/-}$ thymocytes are distinct. *Trp53*$^{-/-}$ lymphomas are driven by point mutations in *Pten* and other tumor-associated loci [56, 101] while *H2afx*$^{-/-}$/ *Trp53*$^{-/-}$ lymphomas are driven by clonal chromosomal translocations [13, 39]. Interestingly, these translocations do not involve the TCRα/δ locus in chromosome 14 or breakpoints at either TCRβ in chromosome 6 or TCRγ in chromosome 13, even though the TCRβ is rearranged in the tumor cells. Instead, Spectral Karyotyping (SKY) analysis of *H2afx*$^{-/-}$/ *Trp53*$^{-/-}$ revealed clonal translocations originated by rejoining of DSBs that presumably occur at "random" sites during periods of rapid cellular proliferation. Similarly, conditional inactivation of H2AX and p53 in double negative thymocytes using an Lck-Cre transgenic mouse model resulted in thymic lymphomas driven by clonal translocations that did not typically involve antigen receptor loci [187]. Finally, although deletion of an H2AX conditional allele in ATM-deficient thymocytes increased the number of RAG-dependent chromosomal translocations *in vitro* [185], it did not accelerate lymphomagenesis *in vivo* [185]. Altogether, these observations suggest that, unlike ATM, H2AX is mostly dispensable for the repair of RAG-dependent DSBs, but becomes limiting at DSBs that arise via other mechanisms, such as replication, oxidation or others. A potential explanation for these

findings is that RAG itself may function to promotes DNA end synapsis, providing an overlapping mechanisms with H2AX (and other foci factors) in this context [11]. This notion also may explain the lack of significant defects in V(D)J recombination in *Mdc1*$^{-/-}$ mice [107].

Similar to *H2afx*$^{-/-}$ mice, *Trp53bp1*$^{-/-}$ mice show decreased thymic size and decreased number of peripheral T cells, including α/β and γ/δ T cells [52], pointing to a defect in maturation. Interestingly, the mechanism driving T cell immunodeficiency in the absence of 53BP1 is unique. While ATM, H2AX and MDC1 function to promote repair across a DSBs, 53BP1 is mainly required for the synapsis of two distant DSBs, a critical step during recombination. Specifically, *Trp53bp1*$^{-/-}$ thymocytes are impaired for V to DJ joining, leading to degradation of persistent coding ends and apoptosis. If the apoptotic response is blunted by breeding to a p53-deficient background, thymic lymphomas are observed [116, 175]. However, most *Trp53bp1*$^{-/-}$/*Trp53*$^{-/-}$ lymphomas are driven by polyploidy or by clonal translocations that spare antigen receptor loci [116, 175].

An epistaxis analysis of ATM and 53BP1 functions at RAG-dependent DSBs was also conducted using a murine model of combined germline deficiency [146]. This work indicated that combined loss aggravates the T cells maturation defect, further reducing thymic output [146]. Moreover, *Atm*$^{-/-}$/*Trp53bp1*$^{-/-}$ mice develop thymic lymphomas earlier in life and with higher penetrance than *Atm*$^{-/-}$ controls [146]. Like *Atm*$^{-/-}$ lymphomas, *Atm*$^{-/-}$/*Trp53bp1*$^{-/-}$ lymphomas are driven by clonal chromosomal translocations involving the TCRα/δ locus [146]. Altogether, these data suggest that H2AX and 53BP1 play modest ATM-independent functions in translocation suppression *in vivo*.

### 6.3.3 RAG-Dependent Break and Translocations in Ataxia-Telangiectasia Patients

The requirement for ATM in the repair of RAG-dependent DSBs is highly conserved in mice and humans. Approximately two thirds of patients with classical A-T have low lymphocyte counts and immunodeficiency [121]. Although both circulating B and T cells are decreased, the most common observation is low number of CD4$^{+}$ T cells with impaired response to mitogens and antigens and anergy [121]. The degree of immunodeficiency varies significantly from one patient to another, but tends to be stable over time. Immunodeficiency tends to be less common in the variant, milder forms of the disease [172].

In addition to lymphopenia, A-T patients show increased predisposition to hematological malignancies. Specifically, the risk of lymphoid but not myeloid malignancies is markedly increased [166]. T cell cancers are more frequent than B cell tumors and include T cell acute lymphoblastic leukemia (ALL), T cell lymphomas and, in older A-T patients, T cell prolymphocytic leukemia (T-PLL) [166] . Cytogenetic analysis indicates that tumor cells typically harbor clonal chromosomal rearrangement involving antigen receptor loci [27], suggesting that they originate during V(D)J recombination.

Childhood T cell ALL is the most common malignancy in A-T and frequently involves clonal translocations involving TCRA/D locus in chromosome 14 or TCRB in chromosome 7 [166]. In humans, the TCRA/D locus is located in chromosome 14 and translocations in A-T leukemias are typically inv(14)(q11q32), or tandem translocations of chromosome 14 with breakpoints at q11 and q32 and del(14)(q11q32) [27]. Older A-T patients can harbor clonal expansions of peripheral T cells with inv(14)(q11;q32) and, in addition, t(14,14)(q11;32.1) and more rarely t(X;14)(q28;q1); some of these patients will develop T cell PLL. In these translocations, the TCRA/D breakpoint at 14q11 is fused with a breakpoint at the TCL1 oncogene at 14q32.1 and at the MTCP1 oncogene at Xq28 [166] [145] [130] [6, 47]. These translocations can be detected in the blood of asymptomatic patients for years [27] and likely evolve to full malignancy upon the acquisition of additional alterations, such as trisomy of 8q containing *C-MYC* and others [27].

Interestingly, over half of non-A-T patients with T-PLL carry a somatic mutation of ATM

[158] and the same TCRA;TLC1 and TCRA;MTCP1 translocations are also recurrent clonal lesions in this setting [49, 163]. These translocation likely drive transformation in both A-T and non A-T patients by placing the *TCL1* or *MTCP1* under the control of the TCRα transcriptional enhancer (Eα) [27]. Similarly, cytogenetic abnormalities involving antigen receptor loci are often present in T cell ALL in the general population [2], suggesting that uncharacterized defects in the DDR or NHEJ may promote leukemogenesis more broadly.

The improvement in supportive care has increased the life expectancy of A-T patients and also uncovered their predisposition to solid tumors in the second and third decades of life [171, 172]. Moreover, patients with the milder, "variant" form of the disease tend to develop solid tumors rather than leukemias typically observed in the classical form of the disease [136, 171]. Future investigations for the presence of fusion transcripts in tumor DNA will help determine whether the role for ATM in translocation suppression may also be relevant in this scenario.

## 6.4 The DDR Suppresses Chromosomal Translocations During Class Switch Recombination

### 6.4.1 Mechanisms of Class Switch Recombination

Upon encounter with antigen, $IgM^+$ B cells undergo CSR to diversify their effector functions by expressing the same variable region as a secondary isotype (i.e., IgG, IgA or IgE). Mechanistically, this process involves a deletional recombination reaction at the immunoglobulin heavy (IgH) chain locus constant region (diagrammed in Fig. 6.3). In particular, activation-induced cytidine deaminase (AID; gene symbol, *AICDA*) [118] works in concert with ubiquitous DNA repair pathways (including Base Excision Repair (BER) and Mismatch Repair (MMR) to introduce DSBs at "Switch" (S) regions upstream of Cμ (encoding IgM) and a downstream $C_H$ exon. AID-dependent DSBs are sensed and signaled via ubiquitous DDR factors, brought together across long chromosomal distances ("synapsed") and rejoined via ubiquitous NHEJ. Completion of the recombination reaction results in deletion of Cμ and expression of the variable region together with Cα, Cε or Cγ (to encode IgA, IgE or IgG, respectively). Intervening DNA is sealed into a circle by NHEJ and eventually lost upon division. The general mechanisms of CSR have been the subject of recent excellent reviews [3, 38, 113, 115].

Successful CSR requires that two distant DSBs are repaired by rejoining to each other rather than via rejoining of DNA ends across each individual DSB, exploiting a general cellular response that promotes DSBs repair *in cis* [67]. As diagrammed in Fig. 6.3, AID is thought to introduce numerous DSBs within each of the two recombining S regions. These concurrent DSBs may be rejoined to either DSBs within the same S region (intra-S region recombination, leading to an internal deletions or "shorter" S region) or to DSBs within the recombining S region (inter-S region recombination, leading to CSR). Studies in wild-type B cells indicate that CSR is normally favored over internal deletion. For example, in a typical B cell activation with α-CD40 antibody and Il-4, over half of the cells undergo CSR. In contrast, less than 10% show intra-S deletions (when assayed by Southern blotting which would not detect small deletions). As described below, mutations in specific DDR components impair end-joining during CSR by decreasing the efficiency of synapsis, while others impair repair (i.e., NHEJ) *per se*.

Like V(D)J recombination, CSR is initiated and completed in the G1 phase of the cell cycle [64]. Consistently, defects for AID or the DDR/NHEJ factors that regulate DSB repair during the G1 phase of the cell cycle impair CSR to variable extent. In this context, ATM and its substrates H2AX and 53BP1 are required for efficient CSR in mice and humans, as described in detail below. In contrast, defects in HR or DDR factors that regulate DSB repair in the replicative phases of the cell cycle do not directly interfere with CSR

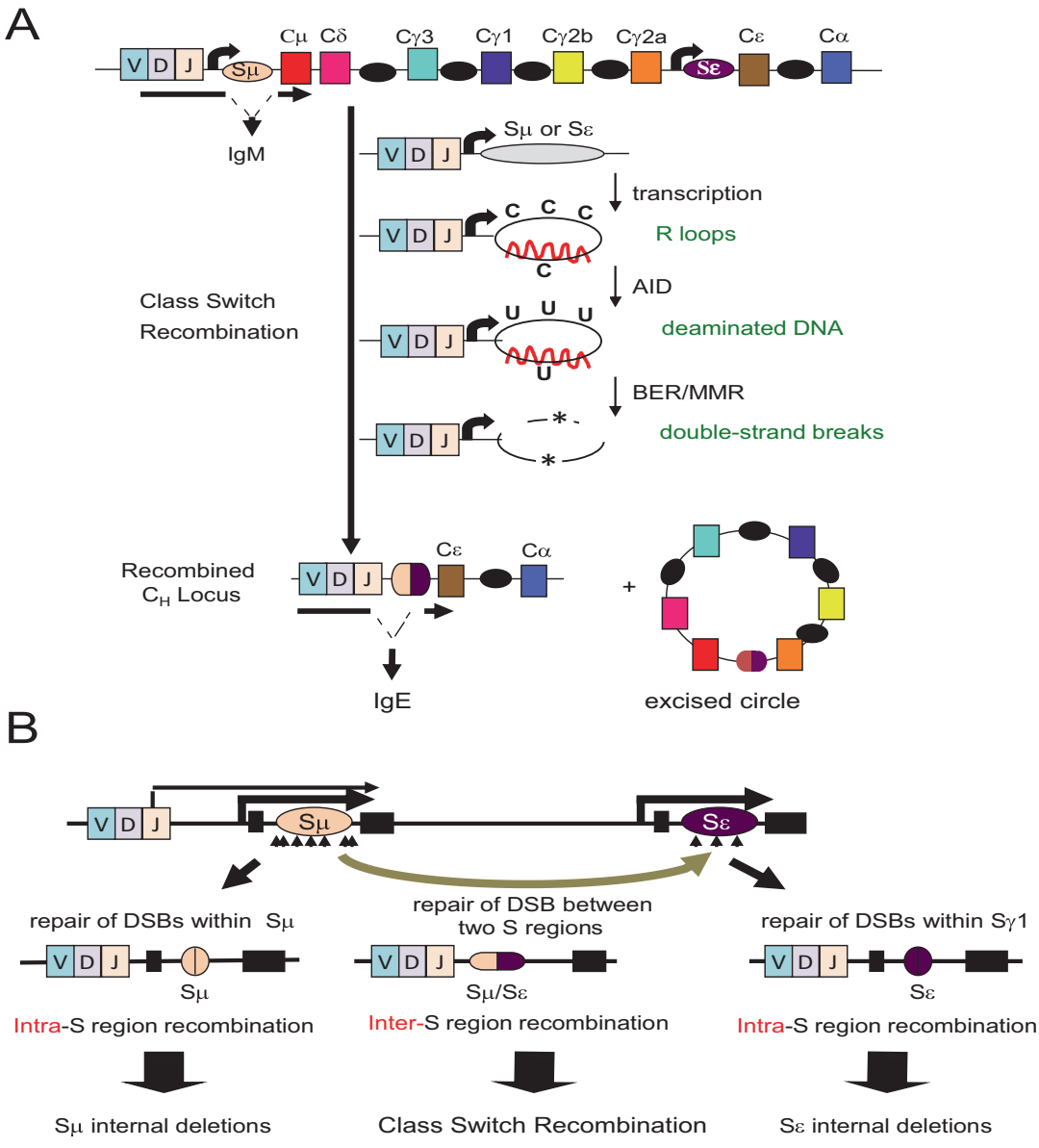


**Fig. 6.3** Mechanisms of Class Switch Recombination (CSR). (**a**) In mature B cells, the $VDJ_H$ exon formed during V(D)J recombination of the immunoglobulin heavy chain (IgH) locus at the pro-B cell stage is initially transcribed with the most upstream exon of the IgH constant region, Cμ, to generate IgM. Upon antigen encounter, mature B cells may undergo CSR to a secondary isotype (such as IgE encoded by the Cε exon in the example depicted here). CSR requires sterile transcription of repetitive "switch" (S) regions upstream of the recombining exons, Sμ and Sε. The nontranscribed strand is preferentially deaminated by AID and processed via ubiquitous DNA repair pathways to generate DNA single-strand breaks (SSBs). Two SSBs in opposite strands are sensed as a double-strand break (DSB) and activate the DNA Damage Response (DDR). DSBs at Sμ and Sε are brought together ("synapsed") and rejoined via the ubiquitous nonhomologous end-joining (NHEJ) pathway to effect recombination. After recombination, the $VDJ_H$ exon is transcribed with the Cε exon, to generate IgE. Intervening DNA is rejoined in a circle and is eventually lost upon replication. (**b**) Possible fates for DSBs generated at S regions of recombining exons during CSR. DSBs within S regions can sometimes rejoin to each other (intra-S region recombination) to form an internal deletion. However, during normal CSR, DSBs within an S region preferentially rejoin to DSBs at another S region (inter-S region recombination), resulting in CSR

and will not be discussed here. Finally, the IgH locus is also modified via programmed lesion-repair cycles in mature B cells undergoing Somatic Hypermutation (SHM). Like CSR, this process employs ubiquitous DNA repair pathways to introduce point mutations into the IgH variable region to increase clonal affinity [51]. However, SHM differs from CSR in that it does not proceed through intermediary DSBs [57, 115]. Consistent with this notion, ATM [122, 123, 137], H2AX [139] and 53BP1 [111] are dispensable for SHM.

### 6.4.2 AID-Dependent Breaks and Translocations in DDR-Deficient Mice

Murine B cells activated for CSR *in vitro* provide a facile system to dissect the genetic requirements for recombination during CSR. The IgH locus heavy chain of B cells residing in the mouse spleen and lymph nodes is mostly in germline configuration ($IgM^+$). Upon isolation and activation with cytokines that mimic either a T cell-independent or a T cell-dependent response, these $IgM^+$ cells proliferate, induce AID and transcription through S regions and switch to a secondary isotype within a few days in a quasi-synchronous manner. Moreover, the efficiency of switching can be readily quantified by flow cytometry after labeling with antibodies that recognize secondary isotypes in the B cell surface. In addition, the highly proliferative nature of these cultures makes them amenable to cytogenetic analysis with IgH locus-specific FISH probes, providing a correlate between the switching defect and the frequency of IgH locus-specific chromosomal breaks and translocations (locus-specific genomic instability; see Fig. 6.4 for schematic of the FISH assay and possible outcomes and interpretation). This experimental pipeline has been applied extensively to understand the contribution of ATM and many of its substrates to the repair of AID-induced DSBs. In general, these studies have found that the molecular events upstream of DSBs (i.e., proliferation, AID induction and S region transcription) occur normally in DDR mutants. Rather, the repair of AID-dependent DSBs is compromised, as described below in more detail.

Analysis of $Atm^{-/-}$ B cells activated for CSR *in vitro* has revealed that the efficiency of switching is reduced to approximately half of the ATM-proficient control cultures [64] [137]. This defect is associated to frequent genomic instability at one or both IgH loci [64], revealing a requirement for ATM in the rejoining of a subset of AID-dependent DSBs. In support of this notion, loss of AID rescues most chromosomal instability at IgH in $Atm^{-/-}$ B cells [34]. Some residual IgH breaks observed in B cells deficient for both ATM and AID is thought to reflect on persistent RAG-dependent DSBs in B cells precursors that fail to trigger apoptosis in the absence of ATM-dependent cell cycle checkpoints [34] and/or when masked as dicentric chromosomes [79]. In $Atm^{-/-}$ activated B cells, IgH locus breaks and translocations are observed frequently (in up to 50% of cells in one study) [64]. Indeed, the most common IgH translocation partner is the broken IgH locus on the other chromosome 12 [64]. Murine chromosomes are acrocentric and therefore the majority of *de novo* rearrangements observed in primary $Atm^{-/-}$ B cell cultures are dicentrics [64, 79, 135]. In addition to IgH-IgH dicentrics, dicentrics with breakpoints at the IgH locus and a chromosomal break elsewhere or between two apparently "random" chromosomal breaks are frequent and often coexist in the same cell [64], highlighting the requirement for ATM in maintaining genomic stability in switching B cells. Moreover, translocations between IgH and c-Myc, a hallmark of many human B cell lymphomas, are detected at low frequency in primary activated $Atm^{-/-}$ B cells [135]. Interestingly, unlike TCRα/δ locus translocations arising in $Atm^{-/-}$ thymocytes, IgH-c-myc translocations in $Atm^{-/-}$ B cells are not clonally selected *in vivo* and $Atm^{-/-}$ mice are not prone to B cell lymphomas [79, 99]. Although the mechanisms underlying these lineage-specific differences are not known, they may relate to differential responses downstream of DSBs that ultimately determine cellular outcomes. In this regard, loss of ATM activates type I interferon signaling [71], a pathway that promotes cell death or survival in a context-dependent manner.

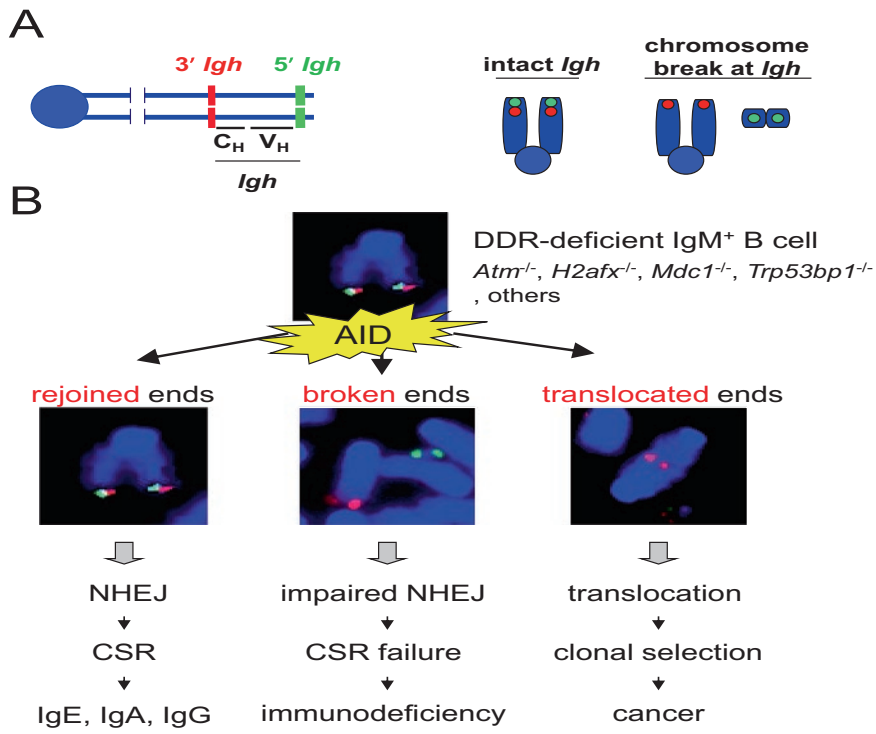


**Fig. 6.4** Analysis of the fate of AID-dependent DNA ends using two-color fluorescence in situ hybridization (FISH) on murine B cell metaphases. (**a**) Schematic of the immunoglobulin heavy chain (IgH) locus in murine chromosome 12. The IgH locus localizes to the subtelomeric region, with the variable region ($V_H$) genes oriented towards the telomere and the constant region ($C_H$) exons oriented towards the centromere. During efficient CSR, rejoining of AID-dependent double-strand breaks (DSB) results in two close-by FISH signals in the subtelomeric region of the chromosome ("intact IgH"). In contrast, failure to rejoin the ends results in "split signals", or localization of each signal to a distinct chromosome fragment. (**b**) B cells were isolated from the spleen of mice deficient for DDR factors and activated for CSR *in vitro* using cytokines. After about three days, the fate of DNA ends was analyzed on metaphase spreads using two-color IgH locus FISH. Rejoining of DNA ends results in close-by signals and indicates recombination and expression of a secondary immunoglobulin isotype (such as IgG, IgE or IgA). However, rejoining is impaired in a subset of DDR-deficient cells, leading to end dissociation and "split signals" (broken or "free" ends). Defective switching manifests clinically as an immunodeficiency characterized by decreased titers of secondary isotypes. Finally, some breaks are repaired aberrantly by rejoining to a break in another chromosome, generating a chromosomal translocation. Most translocations in primary B cells likely have no consequence, but selection for rare oncogenic translocations may promote B cell transformation

ATM likely mediates the formation of γ-H2AX foci at the IgH locus in B cells undergoing CSR [131]. Although DNA-PKcs may also modify H2AX in this context, the ATM-dependent events may serve an important regulatory function by controlling the spread and density of the modification [148]. Like *Atm*$^{-/-}$ B cells, *H2afx*$^{-/-}$ B cells are impaired for CSR to multiple isotypes [64], although the severity of the defect tends to be lesser. Moreover, activated *H2afx*$^{-/-}$ B cells accumulate IgH locus chromosomal breaks and dicentrics with breakpoints at IgH, clearly pointing to a defect in the end-joining phase of CSR. Breeding into AID-deficient mice completely rescues genomic instability at IgH in *H2afx*$^{-/-}$ B cells [64], indicating that these breaks result from switching and excluding their origin as byproducts of transcription, replication or other processes. Finally, although *H2afx*$^{-/-}$ mice develop B cell lymphomas when bred into a p53-deficient background, T cell malignancies are more frequent [13].

The analysis of CSR in murine B cells deficient for 53BP1 (*Trp53bp1*$^{-/-}$ B cells) was particu-

larly gratifying in that it led to novel mechanistic insights into the unique regulation of this process. Unexpectedly, *Trp53bp1*$^{-/-}$ B cells were found to be impaired for CSR to a much greater extent than *Atm*$^{-/-}$ or *H2afx*$^{-/-}$ B cells [111, 177], despite their lesser defect in the repair of "general" chromosomal breaks. The CSR defect is due to defective end-joining of AID-dependent DSBs because IgH locus-specific analysis of activated *Trp53bp1*$^{-/-}$ B cell metaphases revealed frequent IgH breaks [64, 135] that were completely rescued by breeding into an AID-deficient background [135]. However, the mechanism underlying the end-joining defect uniquely relies on defective synapsis of the two recombining DSBs. As a result, *Trp53bp1*$^{-/-}$ B cells show a dramatic increase in the frequency of intra-S switch region recombination [138], presumably reflecting on increased "local" repair in the absence of synapsis. In contrast, activated *H2afx*$^{-/-}$ B cells do not accumulate internal deletions to a greater extent than wild-type B cells [139], suggesting that they fail at rejoining synapsed S regions. In further support of the unique roles for 53BP1 during CSR, others have shown defective synapsis of V and DJ exons during V(D)J recombination of 53BP1-deficient T cells [52] and defective end-joining of dysfunctional telomeres in 53BP1-deficient cells [53].

### 6.4.3 AID-Dependent Breaks and Translocations in A-T Patients

The mechanisms and regulation of CSR are generally conserved between mice and humans [124]. Specifically, a conserved role for ATM in CSR has been demonstrated by the analysis of B cells from A-T patients. Consistent with defective CSR, individuals with A-T show variable decreases in secondary immunoglobulins, most commonly IgG4, IgA, IgE and IgG2, isolated or in combination [121]. These abnormalities are clinically relevant, resulting in impaired antibody response to pathogens and frequent sinopulmonary infections that negatively affect the quality of life of A-T children. Despite these defects, individuals with A-T are not prone to B cell lymphomas but rather to T cell leukemias. These lineage-specific differences in the progression from chromosomal breaks to full malignancy are also observed in the murine models and remain incompletely understood.

Finally, we note that somatic ATM inactivation is common in sporadic mature B cell lymphomas [4, 5, 46, 100, 160, 161]. Deletions at 11q22, containing the ATM locus, occur in approximately half of mantle cell lymphomas (MCLs) [4, 161], a mature B cell malignancy characterized by a clonal T(11,14) that fuses the IgH locus to cyclin D1 to drive its overexpression. The 11q22 deletion in MCL typically leads to loss of ATM function due to mutation of the second allele [35, 150, 161] and correlates with poor clinical outcome [46]. However, the T(11,14) translocation is thought to occur in pro-B cells undergoing V(D)J recombination [86], and may precede the ATM mutation during malignant progression.

ATM mutations are also observed at low frequency in cancers of the breast [1], pancreas [141], bladder [69], prostate [17] and other solid tumors. It currently remains unclear whether ATM roles in translocation suppression may contribute to tumor initiation and/or progression in this context, potentially in cooperation with roles in the activation of cell cycle checkpoints, metabolic regulation and others [97]. Finally, roles for DDR factors other than ATM in translocation suppression in human cancers have not been clearly established, although Bartek and colleagues reported that MDC1 and 53BP1 were lost in a subset of human carcinomas [9]. In summary, the DDR represents a main barrier to transformation in a wide range of human cancers [8, 66] and more work is needed to determine whether its functions in translocation suppression may extend beyond its well-documented roles in hematological malignancies.

## References


1. Ahmed M, Rahman N (2006) ATM and breast cancer susceptibility. Oncogene 25(43):5906–5911. doi:1209873 [pii] https://doi.org/10.1038/sj.onc.1209873
2. Aifantis I, Raetz E, Buonamici S (2008) Molecular pathogenesis of T-cell leukaemia and lymphoma. Nat Rev Immunol 8(5):380–390. https://doi.org/10.1038/nri2304
3. Alt FW, Zhang Y, Meng FL, Guo C, Schwer B (2013) Mechanisms of programmed DNA lesions and genomic instability in the immune system. Cell 152(3):417–429. https://doi.org/10.1016/j.cell.2013.01.007
4. Au WY, Gascoyne RD, Viswanatha DS, Connors JM, Klasa RJ, Horsman DE (2002) Cytogenetic analysis in mantle cell lymphoma: a review of 214 cases. Leuk Lymphoma 43(4):783–791. https://doi.org/10.1080/10428190290016890
5. Austen B, Barone G, Reiman A, Byrd PJ, Baker C, Starczynski J, Nobbs MC, Murphy RP, Enright H, Chaila E, Quinn J, Stankovic T, Pratt G, Taylor AM (2008) Pathogenic ATM mutations occur rarely in a subset of multiple myeloma patients. Br J Haematol 142(6):925–933. https://doi.org/10.1111/j.1365-2141.2008.07281.x
6. Baer R, Heppell A, Taylor AM, Rabbitts PH, Boullier B, Rabbitts TH (1987) The breakpoint of an inversion of chromosome 14 in a T-cell leukemia: sequences downstream of the immunoglobulin heavy chain locus are implicated in tumorigenesis. Proc Natl Acad Sci U S A 84(24):9069–9073
7. Barlow C, Hirotsune S, Paylor R, Liyanage M, Eckhaus M, Collins F, Shiloh Y, Crawley JN, Ried T, Tagle D, Wynshaw-Boris A (1996) Atm-deficient mice: a paradigm of ataxia telangiectasia. Cell 86(1):159–171
8. Bartkova J, Horejsi Z, Koed K, Kramer A, Tort F, Zieger K, Guldberg P, Sehested M, Nesland JM, Lukas C, Orntoft T, Lukas J, Bartek J (2005) DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis. Nature 434(7035):864–870
9. Bartkova J, Horejsi Z, Sehested M, Nesland JM, Rajpert-De Meyts E, Skakkebaek NE, Stucki M, Jackson S, Lukas J, Bartek J (2007) DNA damage response mediators MDC1 and 53BP1: constitutive activation and aberrant loss in breast and lung cancer, but not in testicular germ cell tumours. Oncogene 26(53):7414–7422. https://doi.org/10.1038/sj.onc.1210553
10. Bassing CH, Alt FW (2004a) The cellular response to general and programmed DNA double strand breaks. DNA Repair (Amst) 3(8-9):781–796
11. Bassing CH, Alt FW (2004b) H2AX may function as an anchor to hold broken chromosomal DNA ends in close proximity. Cell Cycle 3(2):149–153
12. Bassing CH, Chua KF, Sekiguchi J, Suh H, Whitlow SR, Fleming JC, Monroe BC, Ciccone DN, Yan C, Vlasakova K, Livingston DM, Ferguson DO, Scully R, Alt FW (2002) Increased ionizing radiation sensitivity and genomic instability in the absence of histone H2AX. Proc Natl Acad Sci U S A 99(12):8173–8178
13. Bassing CH, Suh H, Ferguson DO, Chua KF, Manis J, Eckersdorff M, Gleason M, Bronson R, Lee C, Alt FW (2003) Histone H2AX: a dosage-dependent suppressor of oncogenic translocations and tumors. Cell 114(3):359–370
14. Bekker-Jensen S, Lukas C, Kitagawa R, Melander F, Kastan MB, Bartek J, Lukas J (2006) Spatial organization of the mammalian genome surveillance machinery in response to DNA strand breaks. J Cell Biol 173(2):195–206. https://doi.org/10.1083/jcb.200510130
15. Bekker-Jensen S, Mailand N (2010) Assembly and function of DNA double-strand break repair foci in mammalian cells. DNA Repair (Amst) 9(12):1219–1228. https://doi.org/10.1016/j.dnarep.2010.09.010
16. Bekker-Jensen S, Mailand N (2011) The ubiquitin- and SUMO-dependent signaling response to DNA double-strand breaks. FEBS Lett 585(18):2914–2919. https://doi.org/10.1016/j.febslet.2011.05.056
17. Beltran H, Yelensky R, Frampton GM, Park K, Downing SR, MacDonald TY, Jarosz M, Lipson D, Tagawa ST, Nanus DM, Stephens PJ, Mosquera JM, Cronin MT, Rubin MA (2013) Targeted next-generation sequencing of advanced prostate cancer identifies potential therapeutic targets and disease heterogeneity. Eur Urol 63(5):920–926. https://doi.org/10.1016/j.eururo.2012.08.053
18. Bhandoola A, von Boehmer H, Petrie HT, Zuniga-Pflucker JC (2007) Commitment and developmental potential of extrathymic and intrathymic T cell precursors: plenty to choose from. Immunity 26(6):678–689. https://doi.org/10.1016/j.immuni.2007.05.009
19. Bhargava R, Carson CR, Lee G, Stark JM (2017) Contribution of canonical nonhomologous end joining to chromosomal rearrangements is enhanced by ATM kinase deficiency. Proc Natl Acad Sci U S A 114(4):728–733. https://doi.org/10.1073/pnas.1612204114
20. Bhatia V, Barroso SI, Garcia-Rubio ML, Tumini E, Herrera-Moyano E, Aguilera A (2014) BRCA2 prevents R-loop accumulation and associates with TREX-2 mRNA export factor PCID2. Nature 511(7509):362–365. https://doi.org/10.1038/nature13374
21. Boboila C, Alt FW, Schwer B (2012) Classical and alternative end-joining pathways for repair of lymphocyte-specific and general DNA double-strand breaks. Adv Immunol 116:1–49. https://doi.org/10.1016/B978-0-12-394300-2.00001-6
22. Boder E, Sedgwick RP (1958) Ataxia-telangiectasia; a familial syndrome of progressive cerebellar ataxia, oculocutaneous telangiectasia and frequent pulmonary infection. Pediatrics 21(4):526–554

23. Boerma EG, Siebert R, Kluin PM, Baudis M (2009) Translocations involving 8q24 in Burkitt lymphoma and other malignant lymphomas: a historical review of cytogenetics in the light of todays knowledge. Leukemia 23(2):225–234. https://doi.org/10.1038/leu.2008.281
24. Borghesani PR, Alt FW, Bottaro A, Davidson L, Aksoy S, Rathbun GA, Roberts TM, Swat W, Segal RA, Gu Y (2000) Abnormal development of Purkinje cells and lymphocytes in Atm mutant mice. Proc Natl Acad Sci U S A 97(7):3336–3341
25. Bottini AR, Gatti RA, Wirenfeldt M, Vinters HV (2012) Heterotopic Purkinje cells in ataxia-telangiectasia. Neuropathology 32(1):23–29. https://doi.org/10.1111/j.1440-1789.2011.01210.x
26. Bredemeyer AL, Sharma GG, Huang CY, Helmink BA, Walker LM, Khor KC, Nuskey B, Sullivan KE, Pandita TK, Bassing CH, Sleckman BP (2006) ATM stabilizes DNA double-strand-break complexes during V(D)J recombination. Nature 442(7101):466–470. doi:nature04866 [pii]. https://doi.org/10.1038/nature04866
27. Brito-Babapulle V, Catovsky D (1991) Inversions and tandem translocations involving chromosome 14q11 and 14q32 in T-prolymphocytic leukemia and T-cell leukemias in patients with ataxia telangiectasia. Cancer Genet Cytogenet 55(1):1–9. doi:0165-4608(91)90228-M [pii]
28. Brouwer I, Sitters G, Candelli A, Heerema SJ, Heller I, de Melo AJ, Zhang H, Normanno D, Modesti M, Peterman EJ, Wuite GJ (2016) Sliding sleeves of XRCC4-XLF bridge DNA and connect fragments of broken DNA. Nature 535(7613):566–569. https://doi.org/10.1038/nature18643
29. Brown JS, Jackson SP (2015) Ubiquitylation, neddylation and the DNA damage response. Open Biol 5(4):150018. https://doi.org/10.1098/rsob.150018
30. Bunting SF, Nussenzweig A (2013) End-joining, translocations and cancer. Nat Rev Cancer 13(7):443–454. https://doi.org/10.1038/nrc3537
31. Burma S, Chen BP, Murphy M, Kurimasa A, Chen DJ (2001) ATM phosphorylates histone H2AX in response to DNA double-strand breaks. J Biol Chem 276(45):42462–42467. https://doi.org/10.1074/jbc.C100466200. C100466200 [pii]
32. Butterworth SV, Taylor AM (1986) A subpopulation of t(2;14)(p11;q32) cells in ataxia telangiectasia B lymphocytes. Hum Genet 73(4):346–349
33. Callen E, Bunting S, Huang CY, Difilippantonio MJ, Wong N, Khor B, Mahowald G, Kruhlak MJ, Ried T, Sleckman BP, Nussenzweig A (2009) Chimeric IgH-TCRalpha/delta translocations in T lymphocytes mediated by RAG. Cell Cycle 8(15):2408–2412. doi:9085 [pii]
34. Callen E, Jankovic M, Difilippantonio S, Daniel JA, Chen HT, Celeste A, Pellegrini M, McBride K, Wangsa D, Bredemeyer AL, Sleckman BP, Ried T, Nussenzweig M, Nussenzweig A (2007) ATM prevents the persistence and propagation of chromosome breaks in lymphocytes. Cell 130(1):63–75. doi:S0092-8674(07)00783-0 [pii]. https://doi.org/10.1016/j.cell.2007.06.016
35. Camacho E, Hernandez L, Hernandez S, Tort F, Bellosillo B, Bea S, Bosch F, Montserrat E, Cardesa A, Fernandez PL, Campo E (2002) ATM gene inactivation in mantle cell lymphoma mainly occurs by truncating mutations and missense mutations involving the phosphatidylinositol-3 kinase domain and is associated with increasing numbers of chromosomal imbalances. Blood 99(1):238–244
36. Canela A, Maman Y, Jung S, Wong N, Callen E, Day A, Kieffer-Kwon KR, Pekowska A, Zhang H, Rao SSP, Huang SC, McKinnon PJ, Aplan PD, Pommier Y, Aiden EL, Casellas R, Nussenzweig A (2017) Genome Organization Drives Chromosome Fragility. Cell 170(3):507–521. e518. https://doi.org/10.1016/j.cell.2017.06.034
37. Canman CE, Lim DS, Cimprich KA, Taya Y, Tamai K, Sakaguchi K, Appella E, Kastan MB, Siliciano JD (1998) Activation of the ATM kinase by ionizing radiation and phosphorylation of p53. Science 281(5383):1677–1679
38. Casellas R, Basu U, Yewdell WT, Chaudhuri J, Robbiani DF, Di Noia JM (2016) Mutations, kataegis and translocations in B cells: understanding AID promiscuous activity. Nat Rev Immunol 16(3):164–176. https://doi.org/10.1038/nri.2016.2
39. Celeste A, Difilippantonio S, Difilippantonio MJ, Fernandez-Capetillo O, Pilch DR, Sedelnikova OA, Eckhaus M, Ried T, Bonner WM, Nussenzweig A (2003) H2AX haploinsufficiency modifies genomic stability and tumor susceptibility. Cell 114(3):371–383
40. Celeste A, Petersen S, Romanienko PJ, Fernandez-Capetillo O, Chen HT, Sedelnikova OA, Reina-San-Martin B, Coppola V, Meffre E, Difilippantonio MJ, Redon C, Pilch DR, Olaru A, Eckhaus M, Camerini-Otero RD, Tessarollo L, Livak F, Manova K, Bonner WM, Nussenzweig MC, Nussenzweig A (2002) Genomic instability in mice lacking histone H2AX. Science 296(5569):922–927
41. Chang HHY, Pannunzio NR, Adachi N, Lieber MR (2017) Non-homologous DNA end joining and alternative pathways to double-strand break repair. Nat Rev Mol Cell Biol. https://doi.org/10.1038/nrm.2017.48
42. Chapman JR, Barral P, Vannier JB, Borel V, Steger M, Tomas-Loba A, Sartori AA, Adams IR, Batista FD, Boulton SJ (2013) RIF1 is essential for 53BP1-dependent nonhomologous end joining and suppression of DNA double-strand break resection. Mol Cell. https://doi.org/10.1016/j.molcel.2013.01.002
43. Chen HT, Bhandoola A, Difilippantonio MJ, Zhu J, Brown MJ, Tai X, Rogakou EP, Brotz TM, Bonner WM, Ried T, Nussenzweig A (2000) Response to RAG-mediated VDJ cleavage by NBS1 and gamma-H2AX. Science 290(5498):1962–1965
44. Chiarle R, Zhang Y, Frock RL, Lewis SM, Molinie B, Ho YJ, Myers DR, Choi VW, Compagno M, Malkin DJ, Neuberg D, Monti S, Giallourakis CC,

Gostissa M, Alt FW (2011) Genome-wide translocation sequencing reveals mechanisms of chromosome breaks and rearrangements in B cells. Cell 147(1):107–119. doi:S0092-8674(11)01001-4 [pii]. https://doi.org/10.1016/j.cell.2011.07.049

45. Ciccia A, Elledge SJ (2010) The DNA damage response: making it safe to play with knives. Mol Cell 40(2):179–204. https://doi.org/10.1016/j.molcel.2010.09.019
46. Cuneo A, Bigoni R, Rigolin GM, Roberti MG, Milani R, Bardi A, Minotto C, Agostini P, De Angeli C, Narducci MG, Sabbioni S, Russo G, Negrini M, Castoldi G (2000) Acquired chromosome 11q deletion involving the ataxia teleangiectasia locus in B-cell non-Hodgkin's lymphoma: correlation with clinicobiologic features. J Clin Oncol 18(13):2607–2614
47. Davey MP, Bertness V, Nakahara K, Johnson JP, McBride OW, Waldmann TA, Kirsch IR (1988) Juxtaposition of the T-cell receptor alpha-chain locus (14q11) and a region (14q32) of potential importance in leukemogenesis by a 14;14 translocation in a patient with T-cell chronic lymphocytic leukemia and ataxia-telangiectasia. Proc Natl Acad Sci U S A 85(23):9287–9291
48. Davis MM, Bjorkman PJ (1988) T-cell antigen receptor genes and T-cell recognition. Nature 334(6181):395–402. https://doi.org/10.1038/334395a0
49. Dearden CE (2006) T-cell prolymphocytic leukemia. Med Oncol 23(1):17–22. https://doi.org/10.1385/MO:23:1:17
50. Della-Maria J, Zhou Y, Tsai MS, Kuhnlein J, Carney JP, Paull TT, Tomkinson AE (2011) Human Mre11/human Rad50/Nbs1 and DNA ligase IIIalpha/XRCC1 protein complexes act together in an alternative nonhomologous end joining pathway. J Biol Chem 286(39):33845–33853. https://doi.org/10.1074/jbc.M111.274159
51. Di Noia JM, Neuberger MS (2007) Molecular mechanisms of antibody somatic hypermutation. Annu Rev Biochem 76:1–22. https://doi.org/10.1146/annurev.biochem.76.061705.090740
52. Difilippantonio S, Gapud E, Wong N, Huang CY, Mahowald G, Chen HT, Kruhlak MJ, Callen E, Livak F, Nussenzweig MC, Sleckman BP, Nussenzweig A (2008) 53BP1 facilitates long-range DNA end-joining during V(D)J recombination. Nature 456(7221):529–533. doi:nature07476 [pii]. https://doi.org/10.1038/nature07476
53. Dimitrova N, Chen YC, Spector DL, de Lange T (2008) 53BP1 promotes non-homologous end joining of telomeres by increasing chromatin mobility. Nature 456(7221):524–528. https://doi.org/10.1038/nature07433
54. Dinkelmann M, Spehalski E, Stoneham T, Buis J, Wu Y, Sekiguchi JM, Ferguson DO (2009) Multiple functions of MRN in end-joining pathways during isotype class switching. Nat Struct Mol Biol 16(8):808–813. https://doi.org/10.1038/nsmb.1639
55. Donehower LA, Harvey M, Slagle BL, McArthur MJ, Montgomery CA Jr, Butel JS, Bradley A (1992) Mice deficient for p53 are developmentally normal but susceptible to spontaneous tumours. Nature 356(6366):215–221
56. Dudgeon C, Chan C, Kang W, Sun Y, Emerson R, Robins H, Levine AJ (2014) The evolution of thymic lymphomas in p53 knockout mice. Genes Dev 28(23):2613–2620. https://doi.org/10.1101/gad.252148.114
57. Dudley DD, Chaudhuri J, Bassing CH, Alt FW (2005) Mechanism and Control of V(D)J Recombination versus Class Switch Recombination: Similarities and Differences. Adv Immunol 86:43–112
58. Dujka ME, Puebla-Osorio N, Tavana O, Sang M, Zhu C (2010) ATM and p53 are essential in the cell-cycle containment of DNA breaks during V(D)J recombination in vivo. Oncogene 29(7):957–965. doi:onc2009394 [pii]. https://doi.org/10.1038/onc.2009.394
59. Duquette ML, Pham P, Goodman MF, Maizels N (2005) AID binds to transcription-induced structures in c-MYC that map to regions associated with translocation and hypermutation. Oncogene 24(38):5791–5798. https://doi.org/10.1038/sj.onc.1208746
60. Ehrlich LA, Yang-Iott K, Bassing CH (2014) Tcrdelta translocations that delete the Bcl11b haploinsufficient tumor suppressor gene promote atm-deficient T cell acute lymphoblastic leukemia. Cell Cycle 13(19):3076–3082. https://doi.org/10.4161/15384101.2014.949144
61. Escribano-Diaz C, Orthwein A, Fradet-Turcotte A, Xing M, Young JT, Tkac J, Cook MA, Rosebrock AP, Munro M, Canny MD, Xu D, Durocher D (2013) A cell cycle-dependent regulatory circuit composed of 53BP1-RIF1 and BRCA1-CtIP controls DNA repair pathway choice. Mol Cell. https://doi.org/10.1016/j.molcel.2013.01.001
62. Fang EF, Scheibye-Knudsen M, Chua KF, Mattson MP, Croteau DL, Bohr VA (2016) Nuclear DNA damage signalling to mitochondria in ageing. Nat Rev Mol Cell Biol 17(5):308–321. https://doi.org/10.1038/nrm.2016.14
63. Franco S, Alt FW, Manis JP (2006a) Pathways that suppress programmed DNA breaks from progressing to chromosomal breaks and translocations. DNA Repair (Amst) 5(9-10):1030–1041. doi:S1568-7864(06)00163-7 [pii]. https://doi.org/10.1016/j.dnarep.2006.05.024
64. Franco S, Gostissa M, Zha S, Lombard DB, Murphy MM, Zarrin AA, Yan C, Tepsuporn S, Morales JC, Adams MM, Lou Z, Bassing CH, Manis JP, Chen J, Carpenter PB, Alt FW (2006b) H2AX prevents DNA breaks from progressing to chromosome breaks and translocations. Mol Cell 21(2):201–214
65. Ginno PA, Lott PL, Christensen HC, Korf I, Chedin F (2012) R-loop formation is a distinctive characteristic of unmethylated human CpG island promoters. Mol Cell 45(6):814–825. https://doi.org/10.1016/j.molcel.2012.01.017

66. Gorgoulis VG, Vassiliou LV, Karakaidos P, Zacharatos P, Kotsinas A, Liloglou T, Venere M, Ditullio RA Jr, Kastrinakis NG, Levy B, Kletsas D, Yoneta A, Herlyn M, Kittas C, Halazonetis TD (2005) Activation of the DNA damage checkpoint and genomic instability in human precancerous lesions. Nature 434(7035):907–913
67. Gostissa M, Schwer B, Chang A, Dong J, Meyers RM, Marecki GT, Choi VW, Chiarle R, Zarrin AA, Alt FW (2014) IgH class switching exploits a general property of two DNA breaks to be joined in cis over long chromosomal distances. Proc Natl Acad Sci U S A 111(7):2644–2649. https://doi.org/10.1073/pnas.1324176111
68. Graham TG, Walter JC, Loparo JJ (2016) Two-stage synapsis of DNA ends during non-homologous end joining. Mol Cell 61(6):850–858. https://doi.org/10.1016/j.molcel.2016.02.010
69. Guo G, Sun X, Chen C, Wu S, Huang P, Li Z, Dean M, Huang Y, Jia W, Zhou Q, Tang A, Yang Z, Li X, Song P, Zhao X, Ye R, Zhang S, Lin Z, Qi M, Wan S, Xie L, Fan F, Nickerson ML, Zou X, Hu X, Xing L, Lv Z, Mei H, Gao S, Liang C, Gao Z, Lu J, Yu Y, Liu C, Li L, Fang X, Jiang Z, Yang J, Li C, Zhao X, Chen J, Zhang F, Lai Y, Lin Z, Zhou F, Chen H, Chan HC, Tsang S, Theodorescu D, Li Y, Zhang X, Wang J, Yang H, Gui Y, Wang J, Cai Z (2013) Whole-genome and whole-exome sequencing of bladder cancer identifies frequent alterations in genes involved in sister chromatid cohesion and segregation. Nat Genet 45(12):1459–1463. https://doi.org/10.1038/ng.2798
70. Guo Z, Kozlov S, Lavin MF, Person MD, Paull TT (2010) ATM activation by oxidative stress. Science 330(6003):517–521. doi:330/6003/517 [pii] https://doi.org/10.1126/science.1192912
71. Hartlova A, Erttmann SF, Raffi FA, Schmalz AM, Resch U, Anugula S, Lienenklaus S, Nilsson LM, Kroger A, Nilsson JA, Ek T, Weiss S, Gekara NO (2015) DNA damage primes the type I interferon system via the cytosolic DNA sensor STING to promote anti-microbial innate immunity. Immunity 42(2):332–343. https://doi.org/10.1016/j.immuni.2015.01.012
72. Harvey M, McArthur MJ, Montgomery CA Jr, Bradley A, Donehower LA (1993) Genetic background alters the spectrum of tumors that develop in p53-deficient mice. FASEB J 7(10):938–943
73. Hatchi E, Skourti-Stathaki K, Ventz S, Pinello L, Yen A, Kamieniarz-Gdula K, Dimitrov S, Pathania S, McKinney KM, Eaton ML, Kellis M, Hill SJ, Parmigiani G, Proudfoot NJ, Livingston DM (2015) BRCA1 recruitment to transcriptional pause sites is required for R-loop-driven DNA damage repair. Mol Cell 57(4):636–647. https://doi.org/10.1016/j.molcel.2015.01.011
74. Helmink BA, Bredemeyer AL, Lee BS, Huang CY, Sharma GG, Walker LM, Bednarski JJ, Lee WL, Pandita TK, Bassing CH, Sleckman BP (2009) MRN complex function in the repair of chromosomal Rag-mediated DNA double-strand breaks. J Exp Med 206(3):669–679. https://doi.org/10.1084/jem.20081326
75. Helmink BA, Tubbs AT, Dorsett Y, Bednarski JJ, Walker LM, Feng Z, Sharma GG, McKinnon PJ, Zhang J, Bassing CH, Sleckman BP (2011) H2AX prevents CtIP-mediated DNA end resection and aberrant repair in G1-phase lymphocytes. Nature 469(7329):245–249. doi:nature09585 [pii]. https://doi.org/10.1038/nature09585
76. Helmrich A, Ballarino M, Tora L (2011) Collisions between replication and transcription complexes cause common fragile site instability at the longest human genes. Mol Cell 44(6):966–977. https://doi.org/10.1016/j.molcel.2011.10.013
77. Heppell A, Butterworth SV, Hollis RJ, Kennaugh AA, Beatty DW, Taylor AM (1988) Breakage of the T cell receptor alpha chain locus in non malignant clones from patients with ataxia telangiectasia. Hum Genet 79(4):360–364
78. Hopfner KP, Craig L, Moncalian G, Zinkel RA, Usui T, Owen BA, Karcher A, Henderson B, Bodmer JL, McMurray CT, Carney JP, Petrini JH, Tainer JA (2002) The Rad50 zinc-hook is a structure joining Mre11 complexes in DNA recombination and repair. Nature 418(6897):562–566. doi:https://doi.org/10.1038/nature00922 nature00922 [pii]
79. Hu J, Tepsuporn S, Meyers RM, Gostissa M, Alt FW (2014) Developmental propagation of V(D)J recombination-associated DNA breaks and translocations in mature B cells via dicentric chromosomes. Proc Natl Acad Sci U S A 111(28):10269–10274. https://doi.org/10.1073/pnas.1410112111
80. Huang CY, Sharma GG, Walker LM, Bassing CH, Pandita TK, Sleckman BP (2007) Defects in coding joint formation in vivo in developing ATM-deficient B and T lymphocytes. J Exp Med 204(6):1371–1381. doi:jem.20061460 [pii]. https://doi.org/10.1084/jem.20061460
81. Huen MS, Grant R, Manke I, Minn K, Yu X, Yaffe MB, Chen J (2007) RNF8 transduces the DNA-damage signal via histone ubiquitylation and checkpoint protein assembly. Cell 131(5):901–914. doi:S0092-8674(07)01270-6 [pii]. https://doi.org/10.1016/j.cell.2007.09.041
82. Huertas P, Aguilera A (2003) Cotranscriptionally formed DNA:RNA hybrids mediate transcription elongation impairment and transcription-associated recombination. Mol Cell 12(3):711–721
83. Hustedt N, Durocher D (2016) The control of DNA repair by the cell cycle. Nat Cell Biol 19(1):1–9. https://doi.org/10.1038/ncb3452
84. Jacks T, Remington L, Williams BO, Schmitt EM, Halachmi S, Bronson RT, Weinberg RA (1994) Tumor spectrum analysis in p53-mutant mice. Curr Biol 4(1):1–7
85. Jackson SP, Durocher D (2013) Regulation of DNA damage responses by ubiquitin and SUMO. Mol Cell 49(5):795–807. https://doi.org/10.1016/j.molcel.2013.01.017

86. Jares P, Colomer D, Campo E (2012) Molecular pathogenesis of mantle cell lymphoma. J Clin Invest 122(10):3416–3423. https://doi.org/10.1172/JCI61272
87. Jasin M, Rothstein R (2013) Repair of strand breaks by homologous recombination. Cold Spring Harb Perspect Biol 5(11):a012740. https://doi.org/10.1101/cshperspect.a012740
88. Jiang H, Chang FC, Ross AE, Lee J, Nakayama K, Desiderio S (2005) Ubiquitylation of RAG-2 by Skp2-SCF links destruction of the V(D)J recombinase to the cell cycle. Mol Cell 18(6):699–709. doi:S1097-2765(05)01317-1 [pii]. https://doi.org/10.1016/j.molcel.2005.05.011
89. Jiang W, Lee BJ, Li C, Dubois RL, Gostissa M, Alt FW, Zha S (2015) Aberrant TCRdelta rearrangement underlies the T-cell lymphocytopenia and t(12;14) translocation associated with ATM deficiency. Blood 125(17):2665–2668. https://doi.org/10.1182/blood-2015-01-622621
90. Kamimura K, Ohi H, Kubota T, Okazuka K, Yoshikai Y, Wakabayashi Y, Aoyagi Y, Mishima Y, Kominami R (2007) Haploinsufficiency of Bcl11b for suppression of lymphomagenesis and thymocyte development. Biochem Biophys Res Commun 355(2):538–542. https://doi.org/10.1016/j.bbrc.2007.02.003
91. Kastan MB, Zhan Q, el-Deiry WS, Carrier F, Jacks T, Walsh WV, Plunkett BS, Vogelstein B, Fornace AJ Jr (1992) A mammalian cell cycle checkpoint pathway utilizing p53 and GADD45 is defective in ataxia-telangiectasia. Cell 71(4):587–597
92. Kennaugh AA, Butterworth SV, Hollis R, Baer R, Rabbitts TH, Taylor AM (1986) The chromosome breakpoint at 14q32 in an ataxia telangiectasia t(14;14) T cell clone is different from the 14q32 breakpoint in Burkitts and an inv(14) T cell lymphoma. Hum Genet 73(3):254–259
93. Klein IA, Resch W, Jankovic M, Oliveira T, Yamane A, Nakahashi H, Di Virgilio M, Bothmer A, Nussenzweig A, Robbiani DF, Casellas R, Nussenzweig MC (2011) Translocation-capture sequencing reveals the extent and nature of chromosomal rearrangements in B lymphocytes. Cell 147 (1):95–106. doi:S0092-8674(11)00999-8 [pii]10.1016/j.cell.2011.07.048
94. Kojis TL, Gatti RA, Sparkes RS (1991) The cytogenetics of ataxia telangiectasia. Cancer Genet Cytogenet 56(2):143–156
95. Kojis TL, Schreck RR, Gatti RA, Sparkes RS (1989) Tissue specificity of chromosomal rearrangements in ataxia-telangiectasia. Hum Genet 83(4):347–352
96. Kolas NK, Chapman JR, Nakada S, Ylanko J, Chahwan R, Sweeney FD, Panier S, Mendez M, Wildenhain J, Thomson TM, Pelletier L, Jackson SP, Durocher D (2007) Orchestration of the DNA-damage response by the RNF8 ubiquitin ligase. Science 318(5856):1637–1640. doi:1150034 [pii]. https://doi.org/10.1126/science.1150034
97. Korz C, Pscherer A, Benner A, Mertens D, Schaffner C, Leupolt E, Dohner H, Stilgenbauer S, Lichter P (2002) Evidence for distinct pathomechanisms in B-cell chronic lymphocytic leukemia and mantle cell lymphoma by quantitative expression analysis of cell cycle and apoptosis-associated genes. Blood 99(12):4554–4561
98. Krangel MS, Carabana J, Abbarategui I, Schlimgen R, Hawwari A (2004) Enforcing order within a complex locus: current perspectives on the control of V(D)J recombination at the murine T-cell receptor alpha/delta locus. Immunol Rev 200:224–232. https://doi.org/10.1111/j.0105-2896.2004.00155.x
99. Lavin MF (2013) The appropriateness of the mouse model for ataxia-telangiectasia: neurological defects but no neurodegeneration. DNA Repair (Amst) 12(8):612–619. https://doi.org/10.1016/j.dnarep.2013.04.014
100. Lens D, Matutes E, Catovsky D, Coignet LJ (2000) Frequent deletions at 11q23 and 13q14 in B cell prolymphocytic leukemia (B-PLL). Leukemia 14(3):427–430
101. Liao MJ, Zhang XX, Hill R, Gao J, Qumsiyeh MB, Nichols W, Van Dyke T (1998) No requirement for V(D)J recombination in p53-deficient thymic lymphoma. Mol Cell Biol 18(6):3495–3501
102. Lieber MR (2010) The mechanism of double-strand DNA break repair by the nonhomologous DNA end-joining pathway. Annu Rev Biochem 79:181–211. https://doi.org/10.1146/annurev.biochem.052308.093131
103. Lieber MR (2016) Mechanisms of human lymphoid chromosomal translocations. Nat Rev Cancer 16(6):387–398. https://doi.org/10.1038/nrc.2016.40
104. Lieber MR, Ma Y, Pannicke U, Schwarz K (2003) Mechanism and regulation of human non-homologous DNA end-joining. Nat Rev Mol Cell Biol 4(9):712–720. https://doi.org/10.1038/nrm1202. nrm1202 [pii]
105. Liyanage M, Weaver Z, Barlow C, Coleman A, Pankratz DG, Anderson S, Wynshaw-Boris A, Ried T (2000) Abnormal rearrangement within the alpha/delta T-cell receptor locus in lymphomas from Atm-deficient mice. Blood 96(5):1940–1946
106. Loffert D, Schaal S, Ehlich A, Hardy RR, Zou YR, Muller W, Rajewsky K (1994) Early B-cell development in the mouse: insights from mutations introduced by gene targeting. Immunol Rev 137:135–153
107. Lou Z, Minter-Dykhouse K, Franco S, Gostissa M, Rivera MA, Celeste A, Manis JP, van Deursen J, Nussenzweig A, Paull TT, Alt FW, Chen J (2006) MDC1 maintains genomic stability by participating in the amplification of ATM-dependent DNA damage signals. Mol Cell 21(2):187–200
108. Lovejoy CA, Cortez D (2009) Common mechanisms of PIKK regulation. DNA Repair (Amst) 8(9):1004–1008. https://doi.org/10.1016/j.dnarep.2009.04.006
109. Luo K, Yuan J, Lou Z (2011) Oligomerization of MDC1 protein is important for proper DNA dam-

age response. J Biol Chem 286(32):28192–28199. https://doi.org/10.1074/jbc.M111.258087
110. Mailand N, Bekker-Jensen S, Faustrup H, Melander F, Bartek J, Lukas C, Lukas J (2007) RNF8 ubiquitylates histones at DNA double-strand breaks and promotes assembly of repair proteins. Cell 131(5):887–900. doi:S0092-8674(07)01271-8 [pii]. https://doi.org/10.1016/j.cell.2007.09.040
111. Manis JP, Morales JC, Xia Z, Kutok JL, Alt FW, Carpenter PB (2004) 53BP1 links DNA damage-response pathways to immunoglobulin heavy chain class-switch recombination. Nat Immunol 5(5):481–487
112. Matsuoka S, Ballif BA, Smogorzewska A, McDonald ER, 3rd, Hurov KE, Luo J, Bakalarski CE, Zhao Z, Solimini N, Lerenthal Y, Shiloh Y, Gygi SP, Elledge SJ (2007) ATM and ATR substrate analysis reveals extensive protein networks responsive to DNA damage. Science 316(5828):1160–1166. doi:316/5828/1160 [pii] https://doi.org/10.1126/science.1140321
113. Matthews AJ, Zheng S, DiMenna LJ, Chaudhuri J (2014) Regulation of immunoglobulin class-switch recombination: choreography of noncoding transcription, targeted DNA deamination, and long-range DNA repair. Adv Immunol 122:1–57. https://doi.org/10.1016/B978-0-12-800267-4.00001-8
114. Metcalfe JA, Parkhill J, Campbell L, Stacey M, Biggs P, Byrd PJ, Taylor AM (1996) Accelerated telomere shortening in ataxia telangiectasia. Nat Genet 13(3):350–353. https://doi.org/10.1038/ng0796-350
115. Methot SP, Di Noia JM (2017) Molecular Mechanisms of Somatic Hypermutation and Class Switch Recombination. Adv Immunol 133:37–87. https://doi.org/10.1016/bs.ai.2016.11.002
116. Morales JC, Franco S, Murphy MM, Bassing CH, Mills KD, Adams MM, Walsh NC, Manis JP, Rassidakis GZ, Alt FW, Carpenter PB (2006) 53BP1 and p53 synergize to suppress genomic instability and lymphomagenesis. Proc Natl Acad Sci U S A 103(9):3310–3315
117. Morales JC, Xia Z, Lu T, Aldrich MB, Wang B, Rosales C, Kellems RE, Hittelman WN, Elledge SJ, Carpenter PB (2003) Role for the BRCA1 C-terminal repeats (BRCT) protein 53BP1 in maintaining genomic stability. J Biol Chem 278(17):14971–14977
118. Muramatsu M, Kinoshita K, Fagarasan S, Yamada S, Shinkai Y, Honjo T (2000) Class switch recombination and hypermutation require activation-induced cytidine deaminase (AID), a potential RNA editing enzyme. Cell 102(5):553–563
119. Myers JS, Cortez D (2006) Rapid activation of ATR by ionizing radiation requires ATM and Mre11. J Biol Chem 281(14):9346–9350. https://doi.org/10.1074/jbc.M513265200
120. Nissenkorn A, Levi YB, Vilozni D, Berkun Y, Efrati O, Frydman M, Yahav J, Waldman D, Somech R, Shenhod E, Menascu S, Ben-Zeev B (2011) Neurologic presentation in children with ataxia-telangiectasia: is small head circumference a hallmark of the disease? J Pediatr 159(3):466–471. e461. https://doi.org/10.1016/j.jpeds.2011.02.005
121. Nowak-Wegrzyn A, Crawford TO, Winkelstein JA, Carson KA, Lederman HM (2004) Immunodeficiency and infections in ataxia-telangiectasia. J Pediatr 144(4):505–511. https://doi.org/10.1016/j.jpeds.2003.12.046
122. Pan-Hammarstrom Q, Dai S, Zhao Y, van Dijk-Hard IF, Gatti RA, Borresen-Dale AL, Hammarstrom L (2003) ATM is not required in somatic hypermutation of VH, but is involved in the introduction of mutations in the switch mu region. J Immunol 170(7):3707–3716
123. Pan-Hammarstrom Q, Lahdesmaki A, Zhao Y, Du L, Zhao Z, Wen S, Ruiz-Perez VL, Dunn-Walters DK, Goodship JA, Hammarstrom L (2006) Disparate roles of ATR and ATM in immunoglobulin class switch recombination and somatic hypermutation. J Exp Med 203(1):99–110. https://doi.org/10.1084/jem.20050595
124. Pan-Hammarstrom Q, Zhao Y, Hammarstrom L (2007) Class switch recombination: a comparison between mouse and human. Adv Immunol 93:1–61. https://doi.org/10.1016/S0065-2776(06)93001-6
125. Pandita TK, Pathak S, Geard CR (1995) Chromosome end associations, telomeres and telomerase activity in ataxia telangiectasia cells. Cytogenet Cell Genet 71(1):86–93
126. Panier S, Durocher D (2009) Regulatory ubiquitylation in response to DNA double-strand breaks. DNA Repair (Amst) 8(4):436–443. doi:S1568-7864(09)00008-1 [pii]. https://doi.org/10.1016/j.dnarep.2009.01.013
127. Panier S, Durocher D (2013) Push back to respond better: regulatory inhibition of the DNA double-strand break response. Nat Rev Mol Cell Biol 14(10):661–672. https://doi.org/10.1038/nrm3659
128. Paula-Barbosa MM, Ruela C, Tavares MA, Pontes C, Saraiva A, Cruz C (1983) Cerebellar cortex ultrastructure in ataxia-telangiectasia. Ann Neurol 13(3):297–302. https://doi.org/10.1002/ana.410130312
129. Paull TT (2015) Mechanisms of ATM Activation. Annu Rev Biochem. https://doi.org/10.1146/annurev-biochem-060614-034335
130. Pekarsky Y, Hallas C, Isobe M, Russo G, Croce CM (1999) Abnormalities at 14q32.1 in T cell malignancies involve two oncogenes. Proc Natl Acad Sci U S A 96(6):2949–2951
131. Petersen S, Casellas R, Reina-San-Martin B, Chen HT, Difilippantonio MJ, Wilson PC, Hanitsch L, Celeste A, Muramatsu M, Pilch DR, Redon C, Ried T, Bonner WM, Honjo T, Nussenzweig MC, Nussenzweig A (2001) AID is required to initiate Nbs1/gamma-H2AX focus formation and mutations at sites of class switching. Nature 414(6864):660–665

132. Petiniot LK, Weaver Z, Barlow C, Shen R, Eckhaus M, Steinberg SM, Ried T, Wynshaw-Boris A, Hodes RJ (2000) Recombinase-activating gene (RAG) 2-mediated V(D)J recombination is not essential for tumorigenesis in Atm-deficient mice. Proc Natl Acad Sci U S A 97(12):6664–6669
133. Petiniot LK, Weaver Z, Vacchio M, Shen R, Wangsa D, Barlow C, Eckhaus M, Steinberg SM, Wynshaw-Boris A, Ried T, Hodes RJ (2002) RAG-mediated V(D)J recombination is not essential for tumorigenesis in Atm-deficient mice. Mol Cell Biol 22(9):3174–3177
134. Prakash R, Zhang Y, Feng W, Jasin M (2015) Homologous recombination and human health: the roles of BRCA1, BRCA2, and associated proteins. Cold Spring Harb Perspect Biol 7(4). https://doi.org/10.1101/cshperspect.a016600
135. Ramiro AR, Jankovic M, Callen E, Difilippantonio S, Chen HT, McBride KM, Eisenreich TR, Chen J, Dickins RA, Lowe SW, Nussenzweig A, Nussenzweig MC (2006) Role of genomic instability and p53 in AID-induced c-myc-Igh translocations. Nature 440(7080):105–109
136. Reiman A, Srinivasan V, Barone G, Last JI, Wootton LL, Davies EG, Verhagen MM, Willemsen MA, Weemaes CM, Byrd PJ, Izatt L, Easton DF, Thompson DJ, Taylor AM (2011) Lymphoid tumours and breast cancer in ataxia telangiectasia; substantial protective effect of residual ATM kinase activity against childhood tumours. Br J Cancer 105(4):586–591. https://doi.org/10.1038/bjc.2011.266
137. Reina-San-Martin B, Chen HT, Nussenzweig A, Nussenzweig MC (2004) ATM is required for efficient recombination between immunoglobulin switch regions. J Exp Med 200(9):1103–1110
138. Reina-San-Martin B, Chen J, Nussenzweig A, Nussenzweig MC (2007) Enhanced intra-switch region recombination during immunoglobulin class switch recombination in 53BP1-/- B cells. Eur J Immunol 37(1):235–239. https://doi.org/10.1002/eji.200636789
139. Reina-San-Martin B, Difilippantonio S, Hanitsch L, Masilamani RF, Nussenzweig A, Nussenzweig MC (2003) H2AX is required for recombination between immunoglobulin switch regions but not for intra-switch region recombination or somatic hypermutation. J Exp Med 197(12):1767–1778
140. Robbiani DF, Nussenzweig MC (2013) Chromosome translocation, B cell lymphoma, and activation-induced cytidine deaminase. Annu Rev Pathol 8:79–103. https://doi.org/10.1146/annurev-pathol-020712-164004
141. Roberts NJ, Jiao Y, Yu J, Kopelovich L, Petersen GM, Bondy ML, Gallinger S, Schwartz AG, Syngal S, Cote ML, Axilbund J, Schulick R, Ali SZ, Eshleman JR, Velculescu VE, Goggins M, Vogelstein B, Papadopoulos N, Hruban RH, Kinzler KW, Klein AP (2012) ATM mutations in patients with hereditary pancreatic cancer. Cancer Discov 2(1):41–46. https://doi.org/10.1158/2159-8290.CD-11-0194
142. Rogakou EP, Boon C, Redon C, Bonner WM (1999) Megabase chromatin domains involved in DNA double-strand breaks in vivo. J Cell Biol 146(5):905–916
143. Rothblum-Oviatt C, Wright J, Lefton-Greif MA, McGrath-Morrow SA, Crawford TO, Lederman HM (2016) Ataxia telangiectasia: a review. Orphanet J Rare Dis 11(1):159. https://doi.org/10.1186/s13023-016-0543-7
144. Ruiz JF, Gomez-Gonzalez B, Aguilera A (2011) AID induces double-strand breaks at immunoglobulin switch regions and c-MYC causing chromosomal translocations in yeast THO mutants. PLoS Genet 7(2):e1002009. https://doi.org/10.1371/journal.pgen.1002009
145. Russo G, Isobe M, Gatti R, Finan J, Batuman O, Huebner K, Nowell PC, Croce CM (1989) Molecular analysis of a t(14;14) translocation in leukemic T-cells of an ataxia telangiectasia patient. Proc Natl Acad Sci U S A 86(2):602–606
146. Rybanska-Spaeder I, Reynolds TL, Chou J, Prakash M, Jefferson T, Huso DL, Desiderio S, Franco S (2013) 53BP1 is limiting for NHEJ repair in ATM-deficient model systems that are subjected to oncogenic stress or radiation. Mol Cancer Res 11(10):1223–1234. https://doi.org/10.1158/1541-7786.MCR-13-0252-T
147. Santos-Pereira JM, Aguilera A (2015) R loops: new modulators of genome dynamics and function. Nat Rev Genet 16(10):583–597. https://doi.org/10.1038/nrg3961
148. Savic V, Yin B, Maas NL, Bredemeyer AL, Carpenter AC, Helmink BA, Yang-Iott KS, Sleckman BP, Bassing CH (2009) Formation of dynamic gamma-H2AX domains along broken DNA strands is distinctly regulated by ATM and MDC1 and dependent upon H2AX densities in chromatin. Mol Cell 34(3):298–310. doi:S1097-2765(09)00241-X [pii]. https://doi.org/10.1016/j.molcel.2009.04.012
149. Savitsky K, Bar-Shira A, Gilad S, Rotman G, Ziv Y, Vanagaite L, Tagle DA, Smith S, Uziel T, Sfez S, Ashkenazi M, Pecker I, Frydman M, Harnik R, Patanjali SR, Simmons A, Clines GA, Sartiel A, Gatti RA, Chessa L, Sanal O, Lavin MF, Jaspers NG, Taylor AM, Arlett CF, Miki T, Weissman SM, Lovett M, Collins FS, Shiloh Y (1995) A single ataxia telangiectasia gene with a product similar to PI-3 kinase. Science 268(5218):1749–1753
150. Schaffner C, Idler I, Stilgenbauer S, Dohner H, Lichter P (2000) Mantle cell lymphoma is characterized by inactivation of the ATM gene. Proc Natl Acad Sci U S A 97 (6):2773-2778. doi:https://doi.org/10.1073/pnas.050400997 050400997 [pii]
151. Schatz DG, Swanson PC (2011) V(D)J recombination: mechanisms of initiation. Annu Rev Genet 45:167–202. https://doi.org/10.1146/annurev-genet-110410-132552
152. Schlissel M, Constantinescu A, Morrow T, Baxter M, Peng A (1993) Double-strand signal sequence breaks in V(D)J recombination are blunt, 5′-phos-

phorylated, RAG-dependent, and cell cycle regulated. Genes Dev 7(12B):2520–2532
153. Shiloh Y, Ziv Y (2013) The ATM protein kinase: regulating the cellular response to genotoxic stress, and more. Nat Rev Mol Cell Biol 14(4):197–210
154. Sleckman BP, Bassing CH, Bardon CG, Okada A, Khor B, Bories JC, Monroe R, Alt FW (1998) Accessibility control of variable region gene assembly during T-cell development. Immunol Rev 165:121–130
155. Smilenov LB, Dhar S, Pandita TK (1999) Altered telomere nuclear matrix interactions and nucleosomal periodicity in ataxia telangiectasia cells before and after ionizing radiation treatment. Mol Cell Biol 19(10):6963–6971
156. Soulas-Sprauel P, Rivera-Munoz P, Malivert L, Le Guyader G, Abramowski V, Revy P, de Villartay JP (2007) V(D)J and immunoglobulin class switch recombinations: a paradigm to study the regulation of DNA end-joining. Oncogene 26(56):7780–7791. doi:1210875 [pii]. https://doi.org/10.1038/sj.onc.1210875
157. Spagnolo L, Rivera-Calzada A, Pearl LH, Llorca O (2006) Three-dimensional structure of the human DNA-PKcs/Ku70/Ku80 complex assembled on DNA and its implications for DNA DSB repair. Mol Cell 22(4):511–519
158. Stankovic T, Stewart GS, Byrd P, Fegan C, Moss PA, Taylor AM (2002) ATM mutations in sporadic lymphoid tumours. Leuk Lymphoma 43(8):1563–1571. https://doi.org/10.1080/1042819021000002884
159. Stiff T, O'Driscoll M, Rief N, Iwabuchi K, Lobrich M, Jeggo PA (2004) ATM and DNA-PK function redundantly to phosphorylate H2AX after exposure to ionizing radiation. Cancer Res 64(7):2390–2396
160. Stilgenbauer S, Liebisch P, James MR, Schroder M, Schlegelberger B, Fischer K, Bentz M, Lichter P, Dohner H (1996) Molecular cytogenetic delineation of a novel critical genomic region in chromosome bands 11q22.3-923.1 in lymphoproliferative disorders. Proc Natl Acad Sci U S A 93(21):11837–11841
161. Stilgenbauer S, Winkler D, Ott G, Schaffner C, Leupolt E, Bentz M, Moller P, Muller-Hermelink HK, James MR, Lichter P, Dohner H (1999) Molecular characterization of 11q deletions points to a pathogenic role of the ATM gene in mantle cell lymphoma. Blood 94(9):3262–3264
162. Stirling PC, Hieter P (2016) Canonical DNA repair pathways influence R-loop-driven genome instability. J Mol Biol. https://doi.org/10.1016/j.jmb.2016.07.014
163. Stoppa-Lyonnet D, Soulier J, Lauge A, Dastot H, Garand R, Sigaux F, Stern MH (1998) Inactivation of the ATM gene in T-cell prolymphocytic leukemias. Blood 91(10):3920–3926
164. Stracker TH, Petrini JH (2011) The MRE11 complex: starting from the ends. Nat Rev Mol Cell Biol 12(2):90–103. doi:nrm3047 [pii]. https://doi.org/10.1038/nrm3047
165. Taylor AM, Butterworth SV (1986) Clonal evolution of T-cell chronic lymphocytic leukaemia in a patient with ataxia telangiectasia. Int J Cancer 37(4):511–516
166. Taylor AM, Metcalfe JA, Thick J, Mak YF (1996) Leukemia and lymphoma in ataxia telangiectasia. Blood 87(2):423–438
167. Telatar M, Teraoka S, Wang Z, Chun HH, Liang T, Castellvi-Bel S, Udar N, Borresen-Dale AL, Chessa L, Bernatowska-Matuszkiewicz E, Porras O, Watanabe M, Junker A, Concannon P, Gatti RA (1998) Ataxia-telangiectasia: identification and detection of founder-effect mutations in the ATM gene in ethnic populations. Am J Hum Genet 62(1):86–97. https://doi.org/10.1086/301673
168. Tonegawa S (1983) Somatic generation of antibody diversity. Nature 302(5909):575–581
169. Tresini M, Warmerdam DO, Kolovos P, Snijder L, Vrouwe MG, Demmers JA, van IWF, Grosveld FG, Medema RH, Hoeijmakers JH, Mullenders LH, Vermeulen W, Marteijn JA (2015) The core spliceosome as target and effector of non-canonical ATM signalling. Nature 523(7558):53–58. https://doi.org/10.1038/nature14512
170. Vaziri H, West MD, Allsopp RC, Davison TS, Wu YS, Arrowsmith CH, Poirier GG, Benchimol S (1997) ATM-dependent telomere loss in aging human diploid fibroblasts and DNA damage lead to the post-translational activation of p53 protein involving poly(ADP-ribose) polymerase. EMBO J 16(19):6018–6033. https://doi.org/10.1093/emboj/16.19.6018
171. Verhagen MM, Abdo WF, Willemsen MA, Hogervorst FB, Smeets DF, Hiel JA, Brunt ER, van Rijn MA, Majoor Krakauer D, Oldenburg RA, Broeks A, Last JI, van't Veer LJ, Tijssen MA, Dubois AM, Kremer HP, Weemaes CM, Taylor AM, van Deuren M (2009) Clinical spectrum of ataxia-telangiectasia in adulthood. Neurology 73(6):430–437. https://doi.org/10.1212/WNL.0b013e3181af33bd
172. Verhagen MM, Last JI, Hogervorst FB, Smeets DF, Roeleveld N, Verheijen F, Catsman-Berrevoets CE, Wulffraat NM, Cobben JM, Hiel J, Brunt ER, Peeters EA, Gomez Garcia EB, van der Knaap MS, Lincke CR, Laan LA, Tijssen MA, van Rijn MA, Majoor-Krakauer D, Visser M, van't Veer LJ, Kleijer WJ, van de Warrenburg BP, Warris A, de Groot IJ, de Groot R, Broeks A, Preijers F, Kremer BH, Weemaes CM, Taylor MA, van Deuren M, Willemsen MA (2012a) Presence of ATM protein and residual kinase activity correlates with the phenotype in ataxia-telangiectasia: a genotype-phenotype study. Hum Mutat 33(3):561–571. https://doi.org/10.1002/humu.22016
173. Verhagen MM, Martin JJ, van Deuren M, Ceuterick-de Groote C, Weemaes CM, Kremer BH, Taylor MA, Willemsen MA, Lammens M (2012b) Neuropathology in classical and variant ataxia-telangiectasia. Neuropathology 32(3):234–244. https://doi.org/10.1111/j.1440-1789.2011.01263.x

174. Ward IM, Chen J (2001) Histone H2AX is phosphorylated in an ATR-dependent manner in response to replicational stress. J Biol Chem 276(51):47759–47762. https://doi.org/10.1074/jbc.C100569200
175. Ward IM, Difilippantonio S, Minn K, Mueller MD, Molina JR, Yu X, Frisk CS, Ried T, Nussenzweig A, Chen J (2005) 53BP1 cooperates with p53 and functions as a haploinsufficient tumor suppressor in mice. Mol Cell Biol 25(22):10079–10086
176. Ward IM, Minn K, van Deursen J, Chen J (2003) p53 Binding protein 53BP1 is required for DNA damage responses and tumor suppression in mice. Mol Cell Biol 23(7):2556–2563
177. Ward IM, Reina-San-Martin B, Olaru A, Minn K, Tamada K, Lau JS, Cascalho M, Chen L, Nussenzweig A, Livak F, Nussenzweig MC, Chen J (2004) 53BP1 is required for class switch recombination. J Cell Biol 165(4):459–464
178. Williams RS, Moncalian G, Williams JS, Yamada Y, Limbo O, Shin DS, Groocock LM, Cahill D, Hitomi C, Guenther G, Moiani D, Carney JP, Russell P, Tainer JA (2008) Mre11 dimers coordinate DNA end bridging and nuclease processing in double-strand-break repair. Cell 135(1):97–109. https://doi.org/10.1016/j.cell.2008.08.017
179. Wood LD, Halvorsen TL, Dhar S, Baur JA, Pandita RK, Wright WE, Hande MP, Calaf G, Hei TK, Levine F, Shay JW, Wang JJ, Pandita TK (2001) Characterization of ataxia telangiectasia fibroblasts with extended life-span through telomerase expression. Oncogene 20(3):278–288. https://doi.org/10.1038/sj.onc.1204072
180. Xie A, Kwok A, Scully R (2009) Role of mammalian Mre11 in classical and alternative nonhomologous end joining. Nat Struct Mol Biol 16(8):814–818. https://doi.org/10.1038/nsmb.1640
181. Xu Y, Ashley T, Brainerd EE, Bronson RT, Meyn MS, Baltimore D (1996) Targeted disruption of ATM leads to growth retardation, chromosomal fragmentation during meiosis, immune defects, and thymic lymphoma. Genes Dev 10(19):2411–2422
182. Xu Y, Price BD (2011) Chromatin dynamics and the repair of DNA double strand breaks. Cell Cycle 10(2):261–267. https://doi.org/10.4161/cc.10.2.14543
183. Yang Y, McBride KM, Hensley S, Lu Y, Chedin F, Bedford MT (2014) Arginine methylation facilitates the recruitment of TOP3B to chromatin to prevent R loop accumulation. Mol Cell 53(3):484–497. https://doi.org/10.1016/j.molcel.2014.01.011
184. Yeo AJ, Becherel OJ, Luff JE, Cullen JK, Wongsurawat T, Jenjaroenpun P, Kuznetsov VA, McKinnon PJ, Lavin MF (2014) R-loops in proliferating cells but not in the brain: implications for AOA2 and other autosomal recessive ataxias. PLoS One 9(3):e90219. https://doi.org/10.1371/journal.pone.0090219
185. Yin B, Lee BS, Yang-Iott KS, Sleckman BP, Bassing CH (2012) Redundant and nonredundant functions of ATM and H2AX in alphabeta T-lineage lymphocytes. J Immunol 189(3):1372–1379. https://doi.org/10.4049/jimmunol.1200829
186. Yin B, Savic V, Juntilla MM, Bredemeyer AL, Yang-Iott KS, Helmink BA, Koretzky GA, Sleckman BP, Bassing CH (2009) Histone H2AX stabilizes broken DNA strands to suppress chromosome breaks and translocations during V(D)J recombination. J Exp Med 206(12):2625–2639. https://doi.org/10.1084/jem.20091320
187. Yin B, Yang-Iott KS, Chao LH, Bassing CH (2011) Cellular context-dependent effects of H2ax and p53 deletion on the development of thymic lymphoma. Blood 117(1):175–185. https://doi.org/10.1182/blood-2010-03-273045
188. Yu K, Chedin F, Hsieh CL, Wilson TE, Lieber MR (2003) R-loops at immunoglobulin class switch regions in the chromosomes of stimulated B cells. Nat Immunol 4(5):442–451. https://doi.org/10.1038/ni919
189. Zha S, Bassing CH, Sanda T, Brush JW, Patel H, Goff PH, Murphy MM, Tepsuporn S, Gatti RA, Look AT, Alt FW (2010) ATM-deficient thymic lymphoma is associated with aberrant tcrd rearrangement and gene amplification. J Exp Med 207(7):1369–1380. doi:jem.20100285 [pii]. https://doi.org/10.1084/jem.20100285
190. Zha S, Sekiguchi J, Brush JW, Bassing CH, Alt FW (2008) Complementary functions of ATM and H2AX in development and suppression of genomic instability. Proc Natl Acad Sci U S A 105(27):9302–9306. doi:0803520105 [pii]. https://doi.org/10.1073/pnas.0803520105
191. Zhang Y, Gostissa M, Hildebrand DG, Becker MS, Boboila C, Chiarle R, Lewis S, Alt FW (2010) The role of mechanistic factors in promoting chromosomal translocations found in lymphoid and other cancers. Adv Immunol 106:93–133. doi:S0065-2776(10)06004-9 [pii]. https://doi.org/10.1016/S0065-2776(10)06004-9
192. Zhao Y, Brickner JR, Majid MC, Mosammaparast N (2014) Crosstalk between ubiquitin and other post-translational modifications on chromatin during double-strand break repair. Trends Cell Biol 24(7):426–434. https://doi.org/10.1016/j.tcb.2014.01.005
193. Zhou Y, Lee JH, Jiang W, Crowe JL, Zha S, Paull TT (2017) Regulation of the DNA damage response by DNA-PKcs inhibitory phosphorylation of ATM. Mol Cell 65(1):91–104. https://doi.org/10.1016/j.molcel.2016.11.004