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REVIEW PAPER

MRGing Chromatin Dynamics and Cellular Senescence

Sandra N. Garcia · Olivia Pereira-Smith

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Abstract Normal primary cells have a finite ability to divide in culture and after a number of population doublings enter a state of irreversible cell cycle arrest known as replicative senescence. Several cellular stresses have been shown to induce a senescence-like growth arrest including shortened telomeres, DNA-damaging stresses, and drastic changes in chromatin structure, for example, through histone deacetylase (HDAC) induction. Histones are core components of chromatin which are subject to a number of chemical modifications that influence the dynamic state of chromatin structure. Proper chromatin structure formation is crucial for most DNA-dependent processes including transcription, replication, and repair which have a profound impact on cellular proliferation and senescence. Several genes important for chromatin remodeling such as the tumor suppressors p53 and retinoblastoma (Rb) affect cellular senescence by mediating changes in chromatin structure and gene expression. The *M*orf4-*R*elated *G*ene (MRG) family of transcription factors forms stable interactions with chromatin-modifying complexes including histone acetyltransferase (HAT) and HDAC complexes and interact with Rb. Further, the MRG family was founded by a gene, Mortality Factor on Chromosome 4, capable of inducing senescence in immortalized cell lines. In this paper, we review the role of the MRG family of proteins in chromatin dynamics and cellular senescence.

Keywords NuA4 · Sin3-HDAC1 · Eaf3 · DNA repair · Aging

S. N. Garcia (✉) · O. Pereira-Smith
Department of Cellular and Structural Biology, STCBM 3.100, The University of Texas Health Sciences Center at San Antonio, 15355 Lambda Drive, San Antonio, TX 78245, USA
e-mail: sandyngarcia@gmail.com; sandra.garcia2@utsa.edu

Introduction

Replicative senescence, as originally defined by Hayflick in the 1960s, occurs after primary human fibroblast cells have undergone a finite number of cell divisions, approximately 60–80 population doublings, in culture [1, 2]. Senescence is a state of irreversible cellular growth arrest characterized by the inability of cells to synthesize DNA and proliferate whilst maintaining basic metabolic processes [2]. A hallmark of cellular senescence is a dramatic change in cell morphology, physiology, gene expression, and the increased incidence of senescence-associated heterochromatic foci (SAHF), and other modifications in chromatin structure [3–12]. There is a wealth of evidence indicating that the maintenance of telomere integrity protects cells from cellular senescence; however, space precludes a full summary of these data which have been extensively reviewed elsewhere [5, 13–21]. In this review, we focus on the emerging, but poorly understood, role of the MRG family of proteins in chromatin remodeling and senescence.

Investigators have taken several approaches to study the underlying mechanisms of senescence and have often employed the study of immortal cells, which have escaped senescence, to gain insight into this cellular process. Elegant cell fusion experiments, performed in the early 1980s, showed that fusion between immortalized cell lines and senescent human fibroblasts resulted in a mortal cell hybrid [22–24]. This result demonstrated that senescence is a dominant phenotype and provided the first evidence that senescence is a mechanism of tumor suppression (reviewed in [25]). Through the use of microcell-mediated chromosome transfer, a normal human chromosome 4 was identified as capable of inducing senescence in immortalized cell lines [26]. One gene capable of inducing

senescence in a subset of immortalized cell lines is the *Mor*tality *f*actor on chromosome *4* (MORF4) [27]. MORF4 is the founding member of a large family of transcription factors including the *M*ORF4-*R*elated *G*enes on human chromosome *15* (MRG15) and on the human *X* chromosome (MRGX); a schematic representation of the mammalian MRG family members is shown in Fig. 1 [24, 28]. The exact mechanism by which the MRG family functions in cellular senescence remains to be elucidated; however, current data link the MRG family to chromatin remodeling and senescence, these findings are discussed below.

Chromatin Modification and Senescence

Chromatin (DNA–protein complexes) provides first-order packaging and higher-order compaction of DNA, measuring approximately 2 m in length, within the cell nucleus (reviewed in [29–32]). The first-order packaging of DNA within the nucleus, forming a 10-nm fiber, entails wrapping DNA into nucleosomes consisting of histone H2A, H2B, H3, and H4 dimers. Addition of the linker histone H1 to chromatin promotes formation of higher-order structures known as 30-nm chromatin fibers. Chromatin is a highly alterable structure that regulates most DNA-dependent processes including transcription, replication, recombination, repair, and chromosome dynamics [30].

Histones, core components of chromatin, are basic proteins with N-terminal "tail" domains that protrude from nucleosomes which are subject to a number of chemical modifications (reviewed in [30]). N-terminal histone tails have a high number of positively charged arginine and lysine residues that are post-translationally modified through acetylation, phosphorylation, methylation, ubiquitination, sumoylation, and ADP-ribosylation [30, 33–35]. The positively charged histone tails are neutralized by the addition of an acetyl group resulting in weaker histone-DNA interactions [36–38]. Thus, histone acetylation has often been correlated with the formation of an "open" chromatin structure that facilitates transcriptional activation ([39] and reviewed in [40]). However, acetylation of histone tails can also result in transcriptional repression and, similarly, decreased acetylation can lead to transcriptional activation [41–44]. Likewise, methylation of histones can result in both transcriptional activation and/or repression of a particular genetic target depending on cellular conditions and signals (reviewed in [45]). Therefore, in recent years, it has become clear that it is a combination of post-translational modifications on histones, known as

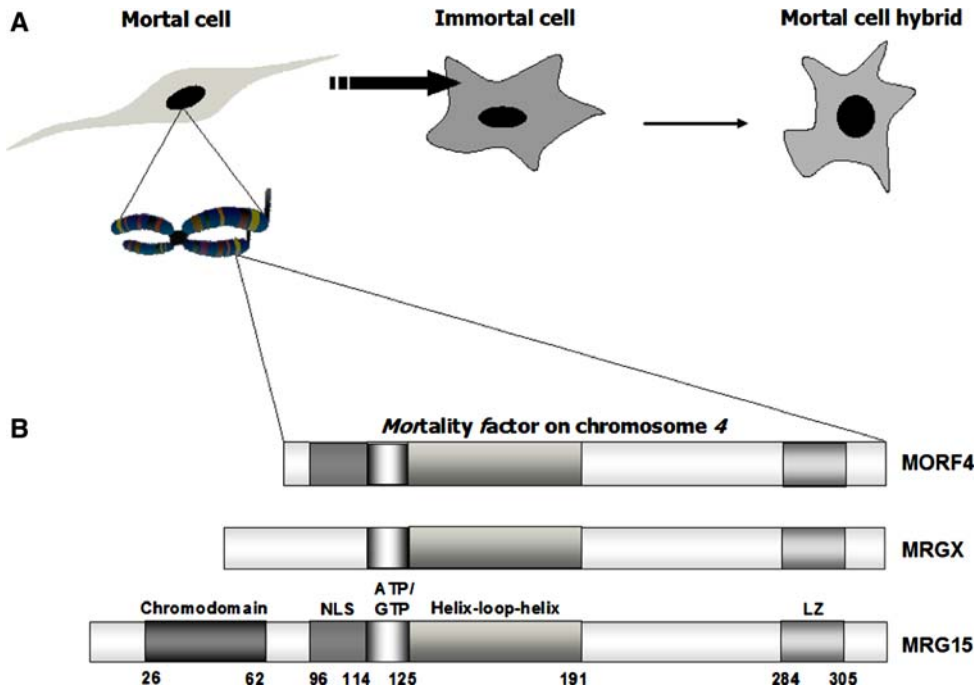

Fig. 1 Senescence is a dominant phenotype. (**a**) Cell fusion experiments between immortalized cell lines and senescent cells revealed that the resulting cell hybrids have a finite life span. Chromosome transfer experiments demonstrated that introduction of a single chromosome (4) induced senescence in a subset of immortalized cell lines. A single gene known as the MORF4 induced senescence when introduced into a subset of immortalized cell lines. (**b**) The MRG family of proteins. MORF4 is the founding member of a family of MRG that plays a role in transcriptional regulation. The family members share evolutionarily conserved nuclear localization signals (NLS), ATP/GTP binding, helix-loop-helix, Leucine zipper, and C-terminal MRG motifs which mediate physical interactions with a number of nucleoproteins including the tumor suppressor Rb, and the Sin3-HDAC and NuA4/KAT5-HAT complexes

the histone code, that dictates a particular transcriptional output, either activation or repression [30]. There are, however, certain specific histone modifications that are more strongly correlated with a particular transcriptional outcome. For example, methylation of histone H3 on Lysines 4, 17, and 36 is correlated with transcriptional activation, whereas methylation of other histone H3 residues including Lysine 9 or Lysine 27 is correlated with transcriptional repression [46–53]. We describe the histone modifications that have been linked to cellular senescence and tissue aging below but wish to state a note of caution at the outset. Senescence is closely related to tissue and organismal aging in that they all share the ability to limit lifespan; however, although there is growing evidence that in vivo tissue aging is caused in part by cellular senescence [54, 55], additional factors contribute to tissue and organismal aging that should be taken into consideration when comparing the mechanisms that underlie these cellular processes (reviewed in [55, 56]).

The histone tail post-translational modifications are numerous, and over 60 marks have been mapped on human linker and core histones thus far. For an updated list of histone modifications refer to the Epigenome Network of Excellence Website: http://www.epigenome-noe.net/resources/scilinks.php (11/2007). Of the number of modifications mapped, only lysine methylation on histones H3 and H4 and acetylation of H4 have been shown to be important modifications in senescence [6, 10, 11, 57, 58]. For example, senescent cells display several heterochromatic domains called SAHF that show a decrease in the linker histone H1 but show enrichment for the H3.3 variant, methylated histone H3 on Lysine 9 (H3K9me) and macro-H2A, a transcriptionally repressive variant of histone H2A [6, 59–61]. The methylated H3K9 marks in SAHF are recognized and bound by the retinoblastoma (Rb) tumor suppressor and by the heterochromatin protein, HP1, which together stably repress transcription of E2F target genes essential for cellular proliferation (reviewed in [62, 63]). Formation of SAHF depends on the Rb pathway as Rb binds stably to the methyltransferase KMT1A (formerly Suv39H1), which targets H3K9, and recruits HP1 to sites of heterochromatin [64]. There are a number of other proteins associated with SAHF, such as the High-Mobility Group A proteins, which are not discussed here but are discussed in detail elsewhere (reviewed in [62, 63]).

In addition to the SAHF-associated histone modification aforementioned, during senescence, the Rb-dependent repression of cell cycle genes has been associated with methylation of H3 at Lysine 9 via the histone methyl transferase (HMTase) KMT1A [6, 12, 65–67]. This histone mark is now considered to be a critical feature of cellular senescence and has been proposed to be a KMT1A-dependent tumor suppressor mechanism that limits oncogenic Ras transformation [57]. Indeed, Ras-induced senescence, also referred to as oncogenic induced senescence (OIS), exhibits SAHF-like chromatin alterations that are abrogated in KMT1A knockout mutants [57]. Besides physically binding to KMT1A, Rb has also been shown to interact with other HMTases, namely KMT5B (formerly Suv4-20H1) and KMT5C (formerly Suv4-20H2) and deletion of the entire Rb family of proteins, which can functionally compensate for one another in MEFs, results in decreased tri-methylation of H4 Lysine 20 which is sufficient for bypassing senescence [58, 64, 68, 69]. Additional studies implicating Rb in senescence are touched on below; however, full treatment of this subject is reviewed elsewhere [18, 63]. A separate study, relevant to tissue aging, analyzed the methylation pattern of histone H4 in different organs derived from rats at various ages and confirmed a role for H4 tri-methylation on Lysine 20 in mammalian aging [12].

Histone acetylation also plays an important role in senescence; studies using high-throughput screening of age-dependent chromatin remodeling and semi-random genome sampling and chromatin immunoprecipitation revealed changes in histone H4 acetylation patterns spanning up to megabase distances when comparing young and old donor-derived fibroblasts [11]. Further, Bandyophadyay et al. [67] have recently shown that induction of the histone deacetylase (HDAC1) in human melanocytic nevi results in the expression of a number of characteristic features of senescence. For example, induction of HDAC1 using a tetracycline-inducible system led to gross deacetylation of histones H3 and H4 and promoted di- and tri-methylation of histone H3 at Lysine 9. In addition, HDAC1 induction also resulted in the formation of Rb/HP1 and HP1/KMT1A foci characteristic of SAHF during heterochromatization in senescence [67]. Therefore, acetylation and methylation of histone tails, that can signal both active and inactive chromatin, are likely to be amongst many, as yet unidentified, modifications made on chromatin that influence gene expression and chromosome dynamics during cellular senescence.

MRG Family and Chromatin Remodeling

The MRG family of proteins share evolutionarily conserved nuclear localization signals (NLS), ATP/GTP binding, helix-loop-helix, Leucine zipper, and C-terminal MRG motifs that mediate physical interactions with a number of nucleoproteins including the tumor suppressor Rb [28, 70–73]. MRG15 is a 37-kDa protein with orthologs found in a wide range of organisms including yeasts and humans [28, 74–77]. MRG15 is unique amongst the family members in that it contains a chromatin-binding

(chromodomain) domain at its N-terminus implicating a role for it in chromatin related functions (Fig. 1) [28, 78]. In contrast, MRGX is a 31-kDa protein, expressed exclusively in mammalian cells, that lacks the chromodomain but is, otherwise, nearly identical to MRG15 (>75% identity) [73, 79]. Both MRG15 and MRGX have been shown to function as transcription factors that modulate activation or repression of the *B-myb* promoter in cell-type dependent manner and, further, tethering a Gal4-Mrg15 fusion protein to a promoter leads to repression of an adjacent reporter gene [73, 80, 81]. Deletion analysis indicated that the chromodomain of MRG15 and the helix-loop-helix and Leucine zipper motifs of both MRG15 and MRGX are necessary for their role in transcriptional regulation [72, 73, 81]. Furthermore, MRG15 and MRGX localize within the cell nucleus and, recently, the MRG proteins have been shown to co-localize with hyperphosphorylated RNA polymerase II at "nuclear subdomains" associated with active transcription elongation [27, 82].

Proteins important for transcriptional regulation often influence a number of cellular processes including cell proliferation and development. Indeed, deletion of *Mrg15* in mice results in gross developmental defects leading to embryonic lethality from 14.5 dpc and primary mouse embryonic fibroblasts (MEFs) derived from *Mrg15* null embryos show defects in cellular proliferation [74]. In contrast, deletion of *MrgX* in mice results in viable and fertile offspring, and *MrgX* null MEFs have similar growth kinetics relative to wild-type MEFs [79]. Interestingly, although *Mrg15* orthologs in *Saccharomyces cerevisiae* and *Caenorhabditis elegans* also contain chromodomains, null mutants of these orthologs are viable reminiscent of *MrgX* null mice. The *Mrg15 C. elegans* ortholog, *mrg-1*, has previously been silenced using RNA-mediated interference resulting in sterile worms with empty gonads, leaky worms characterized with body wall defects, worms with vulval protrusion, and worms with posterior developmental defects [83]. Thus, although *mrg-1* mutants are viable in worms, they are severely hindered at various developmental stages. The function for the MRG family in transcriptional regulation is conserved across species, and recently a function for *mrg-1* in transcriptional activation has been demonstrated in *C. elegans* [84]. Thus, although not important for viability, *mrg-1* plays an important role in nuclear functions that have profound effects on the development and reproduction of *C. elegans.*

Deletion of the *Mrg15* ortholog in *S. cerevisiae*, *EAF3*, results in increased H3 and H4 acetylation at coding sequences and decreased acetylation at promoters leading to equal distribution of histone acetylation levels genomewide [85]. Deletion of *EAF3* also results in the appearance of aberrant transcripts initiating within open reading frames (ORFs) indicating a role for Eaf3 in suppression of transcription initiation within ORFs in a manner similar to that previously shown for the HMTase KMT3A (formerly Set2) in RNA polymerase II-dependent transcription elongation [64, 86–88]. The function for Eaf3 in suppression of promiscuous transcription initiation within ORFs is mediated through its chromodomain which binds methylated histone H3 lysine 36 and targets the deacetylase Rpd3 to nucleosomes within actively transcribed coding regions [88, 89]. Recently, the crystal structure of human MRG15 chromodomain has been solved at a resolution of 2.2 Å [90]. These studies revealed that the MRG15 chromodomain consists of a β-barrel and a long α-helix that resembles the structure of the *Drosophila melanogaster* MOF chromodomain, a member of the MYST family of histone acetyltransferases (HATs). In vitro binding assays demonstrate that, similar to Eaf3, the human MRG15 chromodomain binds to methylated H3 Lysine 36, but does not directly bind methylated H3 at Lysines 4, 9, or 27. These data indicate that the MRG15 chromodomain function is conserved across species [71, 90]. Interestingly, however, in a recent study MRG15 was also shown to indirectly regulate methylation of histone H3 at Lysine 4 through its interaction with the retinoblastoma interacting protein, KDM5A (formerly RBP2) [64, 82]. Therefore, as a component of two distinct nuclear mega-complexes (described below) and in collaboration with its interacting partners, MRG15 is likely to indirectly mediate methylation of Lysines other than Lysine 36 on histone H3.

To date, many studies have indicated that both the MRG15 and MRGX proteins are involved in the regulation of gene expression via chromatin remodeling through association with protein complexes possessing HAT or HDAC activities. Similar to the ING family of proteins implicated in senescence (reviewed in [91]), the *EAF3* yeast ortholog of MRG15 was originally shown to interact with components of, both, the NuA4-HAT and Sin3-Rpd3 (HDAC) complexes in yeast (77, 86, 87, 89]. These observations subsequently led to the discovery that the mammalian MRG15 and MRGX proteins are stable components of the NuA4-KAT5 (formerly Tip60) HAT and Sin3-HDAC complexes, as well as other HAT- and HDAC-possessing complexes, listed in Table 1, in mammalian cells [64, 72, 80, 82, 92, 93]. Despite the fact that MRGX is exclusively expressed in mammalian cells and it does not share the MRG15 chromodomain it, interestingly, shares most of the protein–protein interactions observed for MRG15 across species [72, 80, 82, 92–94].

MRG Family and Senescence

The conundrum, thus far unanswered, that unlike MORF4, MRG15, and MRGX cannot induce replicative senescence

Table 1 MRG15-interacting proteins/complexes

Interacting protein/complex	Cellular function	References
NuA4*KAT5-HAT complex	HAT activity transcriptional regulation, DNA repair	[77, 82, 92, 93]
Sin3-HDAC complex	HDAC activity transcriptional regulation, DNA repair	[82, 86, 87, 89]
Retinoblastoma	Tumor suppressor, mediator of senescence, apoptosis, and quiescence	[72]
*KDM5A, (p130)	Rb binding protein, K-demethylase	[82]
*KAT8	HAT activity DNA repair	[72]
PAM14	Adaptor protein	[70, 72]

Notes: References listed describe the core components of the NuA4 and Sin3-HDAC complexes associated with MRG15 in yeast and human cells and describe the identification of other MRG15-interacting proteins in mammalian cells

*The new nomenclature for chromatin-modifying enzymes (some listed above) was reported during the revision of this manuscript [64]. The former name for KAT5 is Tip60, for KDM5A is RBP2 and for KAT8 is hMOF

when introduced into immortal human cell lines is subject of ongoing research. However, given the striking similarity amongst the three family members, it seems likely that either the N-terminal truncation or the few distinct amino acid residues unique to MORF4 are important for inducing senescence. Deletion analysis and site directed mutagenesis of MRG15 and MRGX are methods currently being employed to test this hypothesis. One formal possibility is that MORF4 can function, in response to specific cell signals, as a dominant negative factor in one or all MRG15 and MRGX functions perhaps by binding to and titrating away interacting proteins. However, the exact mechanism for the difference observed in MRG15 and MRGX versus MORF4 function in inducing senescence remains to be elucidated. The findings discussed below describe the role for MRG15 and MRGX in senescence and tissue aging.

We have discussed the role for MRG15 in cellular proliferation in yeasts, worms, and mice above. Briefly, MRG15 is important for mouse viability and cellular proliferation and important for wild-type development in worms. Therefore, it is interesting that MRG15 is down-regulated in both old mouse livers and in senescent human fibroblasts, and that MRGX is down-regulated in senescent human fibroblasts but are both highly expressed in a broad spectrum of young mouse tissues including heart, blood, lung, brain, testes, and liver, and in young proliferating fibroblasts (O. Pereira-Smith, in preparation). Further, over-expression of MRG15 and MRGX in pre-senescent cells causes them to re-enter the cell cycle (O. Pereira-Smith, in preparation). These studies investigated a classic characteristic of senescence, the inability of cells to synthesize DNA leading to a state of irreversible cellular growth arrest. 5′-bromodeoxyuridine (BrdU)-labeling experiments have shown that pre-senescent cells (~63 PD) have a dramatic decrease in DNA synthesis as evidenced by low levels of BrdU incorporation. Adenoviral-MRG15 and MRGX infection of pre-senescent human fibroblasts results in an increased BrdU-labeling index suggesting that the MRG proteins are able to induce a subset of pre-senescent cells to re-enter the cell cycle (O. Pereira-Smith, in preparation). Furthermore, transient siRNA knock-down of both MRG15 and MRGX in young normal human fibroblasts (~21 PD) results in decreased BrdU incorporation relative to Luciferase control knock-down cells. Analyses to identify molecular mechanisms for the MRG family function in cellular proliferation are currently underway: results may shed additional light on the precise role for this family in senescence and tissue aging.

Additional observations that provide potential links for MRG15 in tissue aging include biochemical analyses of MRG15-complex formation in young versus old mouse livers. Specifically, size exclusion chromatography of nuclear extracts from young and old livers using immunoblotting with antibodies to MRG15 and its interacting partner, HDAC1, revealed that MRG15 co-fractionates with HDAC1 at high-molecular-weight (HMW) fractions in old livers but, in contrast, MRG15 is observed in low-molecular-weight (LMW) fractions away from HDAC1 in young livers (O. Pereira-Smith, in preparation). Similarly, HMW age-specific complexes have been previously described and have shown to contain the senescence-associated proteins Rb and HDAC1 [67, 95]. The Rb shift from LMW in young to HMW fractions in old livers, similar to MRG15, has been correlated with a switch in C/EBPα inhibition of cyclin-dependent kinases to repression of E2F promoters through interaction with Rb [67, 95]. Interestingly, the HDAC1 and HDAC2 proteins, which physically interact with both Rb and MRG15, are always found associated with HMW fractions regardless of age (O. Pereira-Smith, in preparation). Furthermore, induction of HDAC1 in melanocytic nevi results in the redistribution of Rb, and other repressive proteins that regulate tissue aging in mice, such as Brahma-related gene 1 (Brm1) and HP1, to HMW fractions [67, 95–97]. Bandyopadhyay et al.'s findings have uncovered HDAC1 as an important factor in oncogene-induced senescence in melanocytic nevi [67]. As a stable component of the Sin3-HDAC1 complex, and as a direct and indirect regulator of histone H3 methylation,

MRG15 may itself play an important role in this aspect of OIS and/or tissue aging.

Several agents have been shown to induce a senescence-like growth arrest including DNA-damaging stresses such as gamma irradiation and OIS [25, 98, 99]. Senescence induced by these agents that cause DNA double-strand breaks (DSBs) depends on an efficient DNA damage response (DDR) that includes activation of the kinases, ATM and Chk2 [25, 98–100]. A recent study has demonstrated that MRG15 is important for the efficient recruitment of DNA-repair protein, 53BP1, and acetylation of histone H2A.X/H2A at Lysine 5 at sites of damage in MEFs [101]. *Mrg15* mutant MEFs also exhibited defects in growth and DNA repair as assessed by single-cell gel electrophoresis post exposure to gamma irradiation. An early event in response to DNA damage is phosphorylation of the histone H2A.X variant (γ-H2A.X) by the ATM kinase at sites flanking DSBs. Deletion of MRG15 resulted in efficient induction of phosphorylated H2A.X, as assessed by immunoblot analysis; however, as assessed by indirect immunofluorescence of fixed *Mrg15* null versus wild-type MEFs, the foci formation of phosphorylated H2A.X was significantly delayed in *Mrg15* null MEFs compared with wild-type MEFs. Interestingly, removing even a single copy of *Mrg15* ($Mrg15^{+/-}$) in MEFs hindered the response to DNA damage post gamma irradiation, highlighting the importance of a balanced steady-state ratio of functional DNA-repair proteins required for maintaining genomic integrity post exposure to damage [101]. Both the KAT5-HAT and Sin3-HDAC complexes have been shown to play an important role in repair of DSBs [102]. It will be important, in future studies, to delineate the precise role of MRG15 in DNA-repair in the context of its interacting chromatin-modifying complexes. Further, it has recently been proposed that higher incidence of DNA damage through heterozygous defects in the DDR barrier, such as in ATM, BRCA1, BRCA2, p53, and other DNA-repair genes may contribute to senescence [103]. Determining whether decreased MRG15 levels in senescent cells results in hypersensitivity to DNA damage will be of great interest that may further link the MRG family to DDR pathway and senescence.

Conclusion

The MRG family plays an important role in cell proliferation and has been identified in chromatin-modifying complexes possessing HAT and HDAC activities. Thus far, the chromodomain of MRG15 has been shown to preferentially bind to di- and tri-methylated histone H3 Lysine 36 which is associated with regions of active transcription. As a stable component of both HAT and HDAC complexes it will be interesting to determine if the MRG15 chromodomain targets other methylated histone residues that are associated with transcriptional repression. For example, both MRG15 and MRGX physically interact with the tumor suppressor Rb which is important for recruiting HDAC complexes for repression of specific target genes affecting the induction of senescence. Is Rb-mediated repression dependent on recognition and binding of methylated histone residues such as on H4 Lysine 20 or H3 Lysine 9 by the MRG15 chromodomain or through its interacting partners? Are other methyl marks associated with senescence recognized by the MRG15 chromodomain? Do these marks dictate molecular switches between HAT and HDAC activities at specific genomic loci in aged cells? Major questions remain regarding the precise mechanism of the MRG family of proteins in chromatin remodeling and cellular senescence. Learning more about this unique family of proteins will improve our understanding of their role in nuclear function and may provide insight to the intricate lattice of processes that tie chromatin dynamics, including transcription and DNA repair, and cellular senescence.

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