The Biology of Myelodysplastic Syndrome Associated with Isolated del(5q)

5

Martin Jadersten and Aly Karsan

5.1 Introduction

The 5q− syndrome was first described by Van den Berghe et al. in 1974 in three patients with refractory anemia characterized by erythroid hypoplasia, hypolobulated megakaryocytes, normal to elevated platelet counts, and an interstitial deletion on chromosome arm 5q (del[5q]). Isolated del(5q) was the second chromosomal abnormality recognized to be linked to a specific type of malignancy, the first being the Philadelphia chromosome t(9;22) described in 1960. The 5q− syndrome was acknowledged as a separate disease entity in the WHO classification of 2001 (Jaffe et al. 2001) but was renamed myelodysplastic syndrome (MDS) associated with isolated del(5q) in the 2008 version (Swerdlow et al. 2008). Del(5q) also occurs in the patients with more advanced MDS due to blast increase or additional karyotypic changes, as well as in acute myeloid leukemia (AML) and therapy-related MDS. In high-risk patients the presence of del(5q) is associated with adverse prognosis, in sharp contrast to the favorable outcome seen in 5q− syndrome. Intensive efforts have been made to investigate the molecular pathogenesis behind del(5q) MDS, and currently several genes on 5q are thought to be involved in the manifestations of the disease. Recent breakthroughs provide important insights into key aspects of the disease biology and pave the way for treatments effectively targeting the malignant del(5q) clone. This chapter focuses mainly on the classical low-risk 5q− syndrome but also covers more advanced types of MDS with del(5q).

M. Jadersten (✉)
Karolinska University Hospital,
Huddinge Hematology Center M54,
Stockholm SE-141 86, Sweden
e-mail: martin.jadersten@ki.se

A. Karsan, MD (✉)
Department of Genome Sciences,
British Columbia Cancer Research Centre,
675 West 10th Ave., Vancouver, BC V5Z 1L3, Canada
e-mail: akarsan@bcgsc.ca

5.2 Clinical Features

5.2.1 Clinical Presentation

MDS with isolated del(5q) has an insidious onset, with gradually progressing macrocytic anemia, coupled with normal or elevated platelet counts. The bone marrow is characteristically normo- or hypercellular, with erythroid hypoplasia and numerous hypolobulated megakaryocytes (Fig. 5.1). The neutrophil counts are generally normal. Rapidly decreasing granulocyte or platelet counts may reflect disease progression and warrant a repeated marrow investigation. Marrow fibrosis may develop at later stages of the disease.

5.2.2 Cytogenetics

Standard karyotyping shows an isolated interstitial del(5q) that should encompass 5q32–33. The

H.J. Deeg et al., *Myelodysplastic Syndromes*, Hematologic Malignancies,
DOI 10.1007/978-3-642-36229-3_5, © Springer-Verlag Berlin Heidelberg 2013

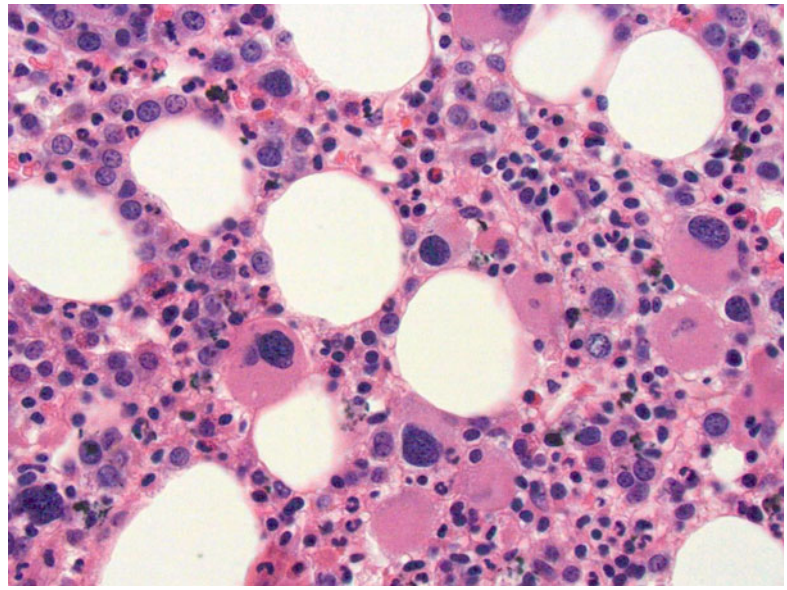

Fig. 5.1 Characteristic bone marrow morphology of MDS with isolated del(5q) demonstrating numerous hypolobulated megakaryocytes

deletion can also be detected by fluorescent in situ hybridization (FISH), which may be of value if karyotyping is unsuccessful. However, karyotyping remains the gold standard for diagnosis and follow-up since it is more sensitive than FISH and has the ability to identify additional abnormalities which may indicate clonal evolution and adverse outcome (Gohring et al. 2011).

5.2.3 Diagnostic Criteria

The WHO 2008 classification defines MDS associated with isolated del(5q) as de novo MDS with less than 5 % bone marrow blasts and isolated del(5q) including the region 5q32–33. Additional criteria are less than 1 % blasts in the peripheral blood and absence of Auer rods, while characteristic marrow morphology or thrombocytosis is not required.

5.2.4 Prognosis

The prognosis is favorable, with median survival of 6–9 years and cumulative probability of evolution to acute myeloid leukemia (AML) of 9–17 % at 5 years (Giagounidis et al. 2004; Giagounidis et al. 2006; Mallo et al. 2011). This relatively favorable outcome is restricted to patients with the classical low-risk 5q− syndrome and does not include patients with additional risk factors.

5.2.5 High-Risk MDS with del(5q)

Additional adverse features such as more than one additional karyotypic abnormality, blast increase ≥5 %, or platelet counts below 100×10^9/l are associated with inferior outcome (Giagounidis et al. 2004; Mallo et al. 2011). The presenting symptoms and the prognosis vary greatly depending on the severity of the alterations. Patients with one additional karyotypic abnormality or blasts elevated to 5–9 % constitute an intermediate-risk group. In MDS with more than 10 % blasts or with therapy-related MDS or AML, del(5q) most frequently occurs in conjunction with complex karyotype and is tightly linked to presence of TP53 mutation (Fidler et al. 2004; Pedersen-Bjergaard et al. 2008) and exceedingly poor outcome.

5.3 Biology of del(5q) MDS

5.3.1 Genes Involved in the Pathogenesis

5.3.1.1 Commonly Deleted Region on Chromosome Arm 5q

There are two distinct commonly deleted regions on 5q (Fig. 5.2). The more distal commonly deleted region (CDR) of 5q− syndrome is defined by a 1.5-megabase region at 5q32–33, containing

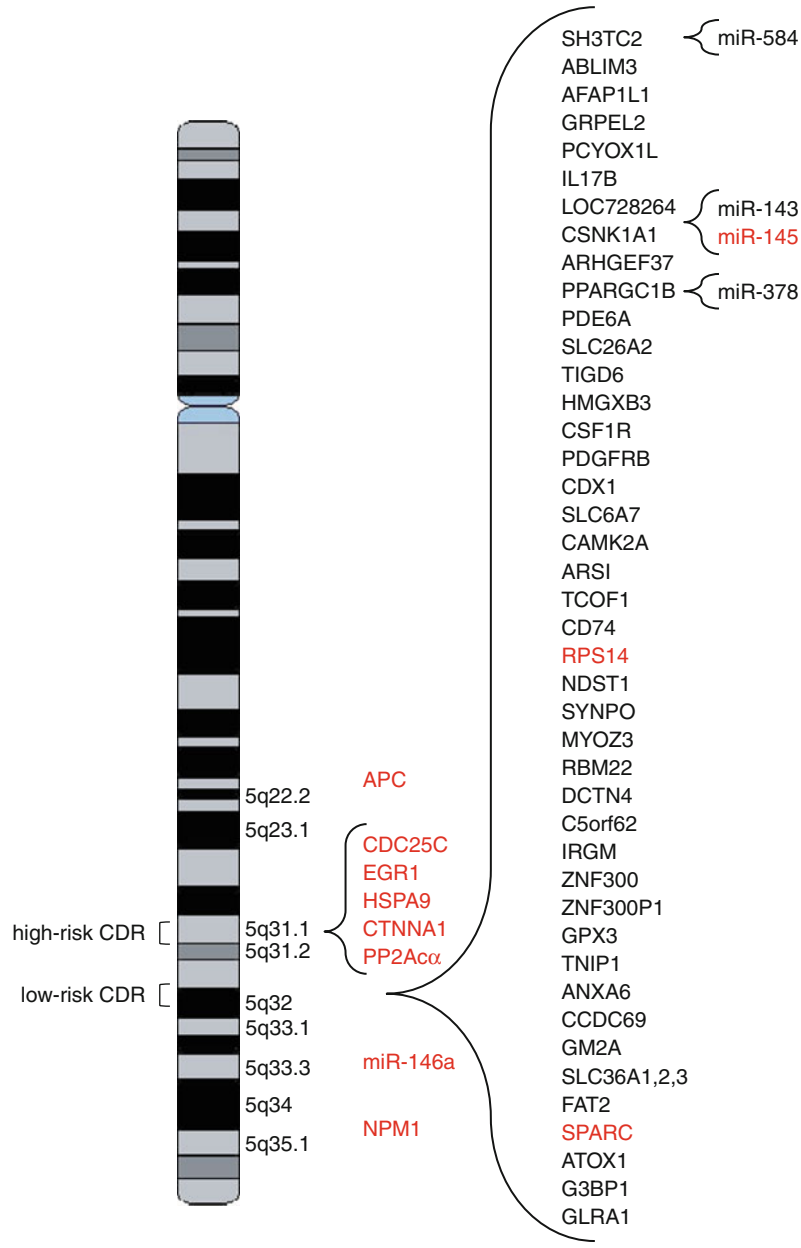

Fig. 5.2 Genes and microRNAs within the low-risk *commonly deleted region* (CDR) at chromosome 5q32–33. The high-risk CDR is also shown; however, only the genes directly implicated in the pathogenesis are listed. Genes potentially disease related, located within or outside the two CDRs, are highlighted in *red*

around 40 coding genes and four microRNAs (Boultwood et al. 2002). No mutations of genes located within the CDR have been identified on the retained allele. This suggests that altered gene dosage may play a role, and recent evidence supports the concept of haploinsufficiency. Functional studies using an RNA interference screen of all genes within the CDR identified ribosomal protein S14 (RPS14) as a haploinsufficient gene responsible for the erythroid failure (Ebert et al. 2008). However, RPS14 haploinsufficiency alone does not explain the megakaryocytic dysplasia and the tendency to thrombocytosis, nor the clonal dominance of del(5q) MDS cells. Examination of noncoding genes at 5q31–5q35 revealed reduced expression of miR-145 and miR-146a in marrow cells from patients with del(5q) MDS (Starczynowski et al. 2010). Depletion of these two microRNAs in mice resulted in variable neutropenia, thrombocytosis, and hypolobulated megakaryocytes with reduced endomitosis in the marrow. These two key

pathogenic mechanisms will be discussed in further detail below.

In patients with high-risk MDS or AML with del(5q), a unique CDR has been delineated at 5q31, centromeric of the low-risk CDR (Zhao et al. 1997; Horrigan et al. 2000). This suggests that other genes are likely to be involved in high-risk disease. It is important to point out that both CDRs are deleted in the majority of low- and high-risk del(5q) MDS patients, indicating that other factors or cooperating mutations elsewhere may be required for disease development.

5.3.1.2 Ribosomal Stress Causes Anemia

Although ribosomes are expressed in all cell types, the dominating feature of ribosomal gene haploinsufficiency is impaired erythropoiesis (Narla and Ebert 2010). This is observed in Diamond-Blackfan anemia, where germline mutations in RPS19 or other ribosomal genes are frequent (Draptchinskaia et al. 1999; Narla and Ebert 2010). In 5q− syndrome, RPS14 is the only gene within the low-risk CDR for which haploinsufficiency has been shown to impair erythropoiesis (Ebert et al. 2008). RPS14 encodes a structural protein of the 40S ribosomal subunit, and its deficiency can cause defects in ribosomal biogenesis and activity (Ebert et al. 2008). The erythroid defect is rescued in vitro by forced expression of RPS14 in hematopoietic stem/progenitor cells from 5q− syndrome patients (Ebert et al. 2008). Haploinsufficiency of RPS14 in mice results in macrocytic anemia and dyserythropoiesis (Barlow et al. 2010). Interestingly, multiple ribosomal genes are downregulated in CD34+ cells of patients with del(5q) MDS, which is consistent with the impaired erythropoiesis being a result of a ribosomal processing defect (Pellagatti et al. 2008). Ribosomal stress due to reduced expression of RPS14 in hematopoietic stem/progenitor cells activates the p53 pathway, inducing the downstream targets p21 and BAX, primarily in the erythroid cell compartment. The mechanism of the observed increase in p53 levels is thought to be increased expression of another ribosomal protein RPL11, which binds the p53 ubiquitin ligase HDM2, thereby preventing p53 ubiquitination and degradation. This results in increased apoptosis and cell cycle arrest (Dutt et al. 2011). Consistent with this finding, crossing mice hemizygous for Rps14 with p53-deficient mice rescues the erythroid progenitor cell defect (Barlow et al. 2010).

5.3.1.3 Reduced miR-145 and miR-146a Expression Induces Innate Immune Signaling

MicroRNAs are small noncoding RNAs, around 22 nucleotides in length, that regulate gene expression by interacting with the 3′ untranslated regions (UTR) of messenger RNAs (mRNAs). MicroRNAs target numerous mRNAs and may induce mRNA degradation and repress protein translation. By interfering with specific cellular pathways, several microRNAs have been shown to have oncogenic properties (Garzon et al. 2009). Knockdown of miR-145 and miR-146a resulted in thrombocytosis and hypolobulated megakaryocytes in the marrow, thus mimicking key features of the 5q− syndrome (Starczynowski et al. 2010). Mice transplanted with marrow depleted for miR-145 and miR-146 succumb to a myeloproliferative/leukemic disorder (Starczynowski et al. 2011). These two microRNAs target genes involved in the innate immune response pathway, including TIRAP (miR-145) and TRAF6 (miR-146a). Transplantation of TRAF6-transduced bone marrow into wild-type mice recapitulated the hematologic phenotype seen with depletion of miR-145/miR-146a including progression to AML or bone marrow failure, suggesting that ectopic activation of innate immune signaling in the hematopoietic stem/progenitor population is a pathogenic feature of del(5q) MDS (Starczynowski et al. 2010). Depletion of miR-145/miR-146a with activation of innate immune signaling results in NF-κB activation and upregulation of IL-6, which is also seen in patients with del(5q) MDS. The platelet and granulocytic defects driven by TRAF6-mediated activation of innate immune signaling and NF-κB are abrogated in mouse marrow cells lacking IL-6, but a similar proportion of mice still develop myeloid neoplasia (Starczynowski et al. 2010). Thus, while the paracrine effects of IL-6 likely explain the thrombocytosis and neutropenia,

clonal dominance of the MDS cells in the marrow appears to be secondary to cell autonomous effects of miR-145/miR-146a haploinsufficiency and deregulated immune signaling.

Recent data indicates that FLI1, another validated target repressed by miR-145, may be of importance for the characteristic megakaryocyte dysplasia and thrombocytosis. FLI1 is an ETS-family transcription factor involved in megakaryocytic differentiation, and its loss results in thrombocytopenia. FLI1 has been shown to be overexpressed in patients with 5q− syndrome, while non-del(5q) MDS patients have levels similar to those of healthy controls. Inhibition of miR-145 or overexpression of FLI1 improves megakaryocyte formation, as seen in patients with 5q− syndrome, while overexpression of miR-145 or inhibition of FLI1 has the reciprocal effect. This suggests that the thrombocytosis observed in patients with 5q− syndrome is due to both cell extrinsic and intrinsic factors. Downregulation of miR-145 or upregulation of FLI1 increased the number of human CD34+ progenitor cells, and knockdown of miR-145 partially rescued the negative effect of RPS14 silencing on the proliferation of progenitor cells in vitro. This further strengthens the evidence that miR-145 is important for clonal dominance (Kumar et al. 2011).

5.3.1.4 Other Candidate Genes Within the CDR

The matricellular protein SPARC is encoded within the low-risk CDR at 5q32–33. It has diverse functions, varying depending on cell type and location. In several malignancies, SPARC acts as a tumor suppressor gene by inhibiting proliferation, angiogenesis, and adhesion to adjacent stroma (Framson and Sage 2004). In del(5q) MDS, SPARC has been shown to be haploinsufficient due to the 5q deletion (Pellagatti et al. 2007), and it is conceivable that this leads to stronger adhesion of the del(5q) hematopoietic stem/progenitor cells to the supporting bone marrow stroma. When CD34+ hematopoietic progenitors are treated with the clinically active drug lenalidomide in vitro, SPARC is upregulated to normal or supranormal levels, thus reversing its haploinsufficiency (Pellagatti et al. 2007). It remains to be demonstrated whether reduced expression of the tumor suppressor gene SPARC plays a role in the pathogenesis of the disease.

5.3.1.5 Genes Implicated in High-Risk del(5q) MDS

Proposed candidate genes within the high-risk CDR at 5q31 include EGR1, HSPA9, and CTNNA1. EGR1-deficient mice treated with an alkylating agent frequently developed myeloproliferative neoplasias coupled with ineffective erythropoiesis and thrombocytopenia (Joslin et al. 2007). Knockdown of HSPA9 in primary human hematopoietic cells or in a murine model impaired erythroid maturation and suppressed hematopoietic cell expansion (Chen et al. 2011). Thus, haploinsufficiency of HSPA9 may play a role in the ineffective hematopoiesis observed in del(5q) MDS but fails to explain the clonal dominance. Forced expression of CTNNA1 in the myeloid cell line HL-60 resulted in reduced proliferation and increased apoptosis, suggesting that haploinsufficiency of this tumor suppressor may provide a growth advantage contributing to the clonal advantage of the del(5q) cells CTNNA1 (Liu et al. 2007).

Several genes outside the two CDRs have also been implicated in myeloid disorders. The gene APC resides more centromeric at 5q21–22 but is generally part of the deletion. APC deficiency leads to ineffective hematopoiesis and loss of HSC quiescence, conceivably contributing to the observed pathology (Lane et al. 2010; Wang et al. 2010). NPM1 is located telomeric of the CDR (at 5q35) and is rarely part of the del(5q) in low-risk MDS, while it is deleted in 40 % of high-risk MDS with del(5q) (La Starza et al. 2010; Pellagatti et al. 2011). Haploinsufficiency of NPM1 is tightly linked to genomic instability and complex karyotype in MDS and AML, likely due to impaired centrosome duplication and inhibition of the tumor suppressors ARF1 and TP53 (Falini et al. 2007). Mice that are heterozygous for Npm1 develop a hypercellular marrow with prominent erythroid and megakaryocytic dysplasia. Moreover, they were prone to develop malignancies, in particular myeloid leukemias, that were associated with

centrosome amplification and chromosomal abnormalities (Grisendi et al. 2005; Sportoletti et al. 2008). In contrast, patients with de novo AML and NPM1 mutations are characterized by normal karyotype (Falini et al. 2005), likely attributable to retained ability to duplicate the centrosome by the mutated NPM1 (Falini et al. 2007). Recently, a transgenic mouse model overexpressing mutated NPM1 resulted in myeloproliferation, suggesting that the NPM1 mutation per se contributes to clonal advantage (Cheng et al. 2010).

5.3.2 Originates in Hematopoietic Stem Cells

In MDS with del(5q) more than 90 % of the CD34+CD38−CD90+ hematopoietic stem cells (HSC) carry the deletion (Nilsson et al. 2000). Further, del(5q) may appear in B and NK cells (Jaju et al. 2000; Nilsson et al. 2000; Kiladjian et al. 2006), and the disease may transform to acute lymphoblastic leukemia. Thus, the disease is considered to originate at the pluripotent HSC level. Despite the fact that the bone marrow is normo- or hypercellular and the stem cell compartment is dominated by del(5q) cells, the marrow fails to release sufficient blood cells into circulation. One contributing factor may be that del(5q) HSCs contain limited long-term culture-initiating assay activity and fail to reconstitute transplanted mice over the long term, reflecting the observed ineffective hematopoiesis (Nilsson et al. 2000). In colony-forming assays in particular, the erythroid colonies are reduced, potentially due to the RPS14 haploinsufficiency (Tehranchi et al. 2010). Despite this impaired function, the gene expression profile of del(5q) and normal HSCs is highly similar. Intriguing exceptions include upregulation of the critical stem cell renewal factor BMI1 and the Notch-signaling inhibitor DLK1 in the HSC fraction and downregulation of the myeloid transcription factor CEBPA at the progenitor stage. The differentially expressed genes differed substantially between HSCs (CD34+CD38−CD90+) and progenitor cells (CD34+CD38+CD90−), stressing the importance of studying homogenous and relevant populations when drawing conclusions about the mechanisms of the disease (Nilsson et al. 2007).

5.3.3 Defects in the Bone Marrow Microenvironment

Evidence suggests that the bone marrow stroma is deficient in del(5q) MDS, resulting in impaired ability to support growth of normal hematopoietic progenitors. The cytokine profile in low-risk MDS marrow plasma is altered, including increased level of TNF-α which is likely to suppress hematopoiesis (Gersuk et al. 1998). It is possible that these alterations are caused by macrophages or other cells that are part of the del(5q) malignant clone and that this may favor the expansion of the malignant over normal cells. There are contradicting data regarding the presence of genetic alterations in stromal cells from patients with del(5q) MDS. Several groups have reported cytogenetic aberrations in mesenchymal cells; however, the genetic changes were generally unrelated to those observed in the MDS cells (Blau et al. 2007; Lopez-Villar et al. 2009). Other groups do not observe genetic alterations in the stromal cells (Soenen-Cornu et al. 2005; Ramakrishnan et al. 2006). Also, allogeneic stem cell transplantation may cure del(5q) MDS, arguing against an inherent stromal defect.

5.4 Novel Prognostic Markers

5.4.1 TP53 Mutation Associated with Leukemic Transformation

Mutations in the tumor suppressor gene TP53 occur in 5–10 % of patients with low-risk MDS and in 10–15 % with high-risk disease. TP53 mutations were until recently thought to be rare in low-risk del(5q) MDS, which stands in contrast to the high frequency observed in MDS patients with complex karyotype that includes del(5q), where around 80 % are mutated (Fidler et al. 2004; Pedersen-Bjergaard et al. 2008). A recent study using deep sequencing demonstrated that 18 % of patients with low-risk del(5q) MDS had TP53

mutation (Jadersten et al. 2011). Interestingly, in more than half of the mutated patients, the clone size was below 20 % and would thus probably not have been detected by conventional Sanger sequencing. TP53 mutation was significantly associated with increased risk of leukemic transformation, in agreement with results in other types of MDS (Padua et al. 1998). When deep sequencing becomes part of the routine workup in MDS, then TP53 mutation is likely to constitute an important prognostic factor.

5.5 Lenalidomide Treatment of del(5q) MDS

5.5.1 Potent Clinical Effect

Lenalidomide has unparalleled efficacy in transfusion-dependent low-risk MDS with del(5q), with 67 % reaching transfusion independence and 45 % complete cytogenetic remission (List et al. 2006). Important side effects include grade III/IV neutropenia and thrombocytopenia. The median response duration is around 2 years. A recent study demonstrated that del(5q) HSCs are relatively insensitive to the effects of lenalidomide. In patients with karyotypic complete cytogenetic remission and no del(5q) detectable by FISH in the CD34+CD38+CD90− progenitor compartment, del(5q) cells were still detectable although at lower levels in all patients studied in the CD34+CD38−CD90+ HSCs fraction. This relative insensitivity of the del(5q) HSCs to lenalidomide suggests that this therapy is unlikely to be curative (Tehranchi et al. 2010). However, it is important to stress that this does not rule out that a large proportion of the patients may have a substantial clinical benefit of the treatment, with durable transfusion independency. Recent safety concerns have been raised, since an unexpectedly high fraction of patients treated with lenalidomide have undergone clonal evolution, with acquisition of complex karyotypes or transformation to AML (Gohring et al. 2010; Jadersten et al. 2011). Therefore, it is advised that even low-risk del(5q) MDS patients treated with lenalidomide are followed closely for signs of disease progression, in particular if they are of transplantable age (Jadersten and Karsan 2011).

5.5.2 Mechanisms of Action

Lenalidomide inhibits numerous cytokines, including IL-6 and TNF-α, and activates T cells and NK cells (Bartlett et al. 2004). After successful treatment with lenalidomide, the stromal defect described above is reversed (Ximeri et al. 2010). This improved function of the stroma may be a direct effect of the treatment or an indirect via suppression of the malignant MDS clone. Other functions ascribed to lenalidomide include inhibition of the cell cycle-regulating phosphatases CDC25C and PP2Acα (Wei et al. 2009). Both these genes are located centromeric to the 5q32–33 CDR but are deleted in most del(5q) MDS patients (Fig. 5.3), potentially contributing to the increased sensitivity of del(5q) cells to lenalidomide. The tumor suppressor gene SPARC was one of four genes significantly upregulated by lenalidomide in vitro and the only one located within the 5q32–33 CDR (Pellagatti et al. 2007). In addition, emerging data indicates that lenalidomide increases miR-143 and miR-145 expression in CD34+ del(5q) progenitors, thus counteracting the haploinsufficiency. This induction may be associated with subsequent clinical response to treatment (Venner et al. 2010). It remains to be resolved which mechanisms are most important for the effects observed in patients with del(5q) MDS.

5.6 Future Directions

Important parts of the pathogenesis of del(5q) MDS have been unraveled; however, it remains to be demonstrated if they are sufficient to induce the disease or if cooperating genetic events are required. Whole genome sequencing is a powerful tool that can address this question. Development of improved mouse models of the disease is also needed to refine our understanding of the disease biology. Efforts to develop targeted therapy are ongoing, exploring approaches such

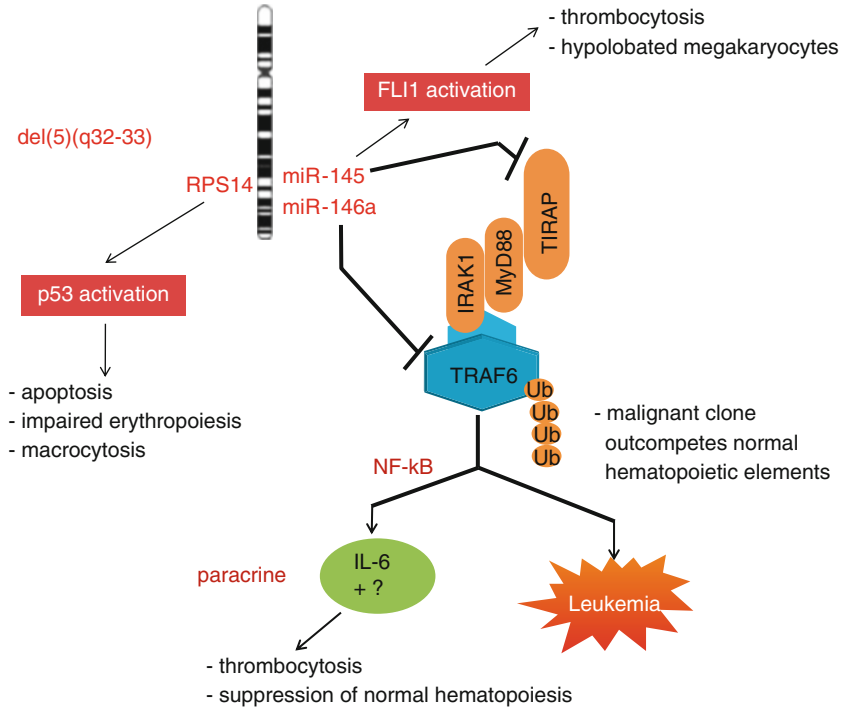

Fig. 5.3 Overview of the biology of MDS with del(5q)

as inhibition of p53 to improve the expansion of del(5q) erythroblasts to alleviate the anemia and inhibition of PP2A to inhibit the malignant clone itself. Deep sequencing of key prognostic genes such as TP53 is likely to improve initial risk stratification and will enable genetic monitoring of emerging adverse subclones in the marrow during the course of the disease. This will be important for optimizing the timing of intensified therapy or allogeneic stem cell transplantation.

References

Barlow JL, Drynan LF, Hewett DR, Holmes LR, Lorenzo-Abalde S, Lane AL, Jolin HE, Pannell R, Middleton AJ, Wong SH, Warren AJ, Wainscoat JS, Boultwood J, McKenzie AN (2010) A p53-dependent mechanism underlies macrocytic anemia in a mouse model of human 5q− syndrome. Nat Med 16(1):59–66

Bartlett JB, Dredge K, Dalgleish AG (2004) The evolution of thalidomide and its IMiD derivatives as anticancer agents. Nat Rev Cancer 4(4):314–322

Blau O, Hofmann WK, Baldus CD, Thiel G, Serbent V, Schumann E, Thiel E, Blau IW (2007) Chromosomal aberrations in bone marrow mesenchymal stroma cells from patients with myelodysplastic syndrome and acute myeloblastic leukemia. Exp Hematol 35(2):221–229

Boultwood J, Fidler C, Strickson AJ, Watkins F, Gama S, Kearney L, Tosi S, Kasprzyk A, Cheng JF, Jaju RJ, Wainscoat JS (2002) Narrowing and genomic annotation of the commonly deleted region of the 5q− syndrome. Blood 99(12):4638–4641

Chen TH, Kambal A, Krysiak K, Walshauser MA, Raju G, Tibbitts JF, Walter MJ (2011) Knockdown of Hspa9, a del(5q31.2) gene, results in a decrease in hematopoietic progenitors in mice. Blood 117(5):1530–1539

Cheng K, Sportoletti P, Ito K, Clohessy JG, Teruya-Feldstein J, Kutok JL, Pandolfi PP (2010) The cytoplasmic NPM mutant induces myeloproliferation in a transgenic mouse model. Blood 115(16):3341–3345

Draptchinskaia N, Gustavsson P, Andersson B, Pettersson M, Willig TN, Dianzani I, Ball S, Tchernia G, Klar J, Matsson H, Tentler D, Mohandas N, Carlsson B, Dahl N (1999) The gene encoding ribosomal protein S19 is mutated in Diamond-Blackfan anaemia. Nat Genet 21(2):169–175

Dutt S, Narla A, Lin K, Mullally A, Abayasekara N, Megerdichian C, Wilson FH, Currie T, Khanna-Gupta A, Berliner N, Kutok JL, Ebert BL (2011) Haploinsufficiency for ribosomal protein genes causes selective activation of p53 in human erythroid progenitor cells. Blood 117(9):2567–2576

Ebert BL, Pretz J, Bosco J, Chang CY, Tamayo P, Galili N, Raza A, Root DE, Attar E, Ellis SR, Golub TR (2008)

Identification of RPS14 as a 5q− syndrome gene by RNA interference screen. Nature 451(7176):335–339

Falini B, Mecucci C, Tiacci E, Alcalay M, Rosati R, Pasqualucci L, La Starza R, Diverio D, Colombo E, Santucci A, Bigerna B, Pacini R, Pucciarini A, Liso A, Vignetti M, Fazi P, Meani N, Pettirossi V, Saglio G, Mandelli F, Lo-Coco F, Pelicci PG, Martelli MF (2005) Cytoplasmic nucleophosmin in acute myelogenous leukemia with a normal karyotype. N Engl J Med 352(3):254–266

Falini B, Nicoletti I, Martelli MF, Mecucci C (2007) Acute myeloid leukemia carrying cytoplasmic/mutated nucleophosmin (NPMc + AML): biologic and clinical features. Blood 109(3):874–885

Fidler C, Watkins F, Bowen DT, Littlewood TJ, Wainscoat JS, Boultwood J (2004) NRAS, FLT3 and TP53 mutations in patients with myelodysplastic syndrome and a del(5q). Haematologica 89(7):865–866

Framson PE, Sage EH (2004) SPARC and tumor growth: where the seed meets the soil? J Cell Biochem 92(4):679–690

Garzon R, Calin GA, Croce CM (2009) MicroRNAs in cancer. Annu Rev Med 60:167–179

Gersuk GM, Beckham C, Loken MR, Kiener P, Anderson JE, Farrand A, Troutt AB, Ledbetter JA, Deeg HJ (1998) A role for tumour necrosis factor-alpha, Fas and Fas-Ligand in marrow failure associated with myelodysplastic syndrome. Br J Haematol 103(1): 176–188

Giagounidis AA, Germing U, Haase S, Hildebrandt B, Schlegelberger B, Schoch C, Wilkens L, Heinsch M, Willems H, Aivado M, Aul C (2004) Clinical, morphological, cytogenetic, and prognostic features of patients with myelodysplastic syndromes and del(5q) including band q31. Leukemia 18(1):113–119

Giagounidis AA, Germing U, Aul C (2006) Biological and prognostic significance of chromosome 5q deletions in myeloid malignancies. Clin Cancer Res 12(1):5–10

Gohring G, Giagounidis A, Busche G, Kreipe HH, Zimmermann M, Hellstrom-Lindberg E, Aul C, Schlegelberger B (2010) Patients with del(5q) MDS who fail to achieve sustained erythroid or cytogenetic remission after treatment with lenalidomide have an increased risk for clonal evolution and AML progression. Ann Hematol 89(4):365–374

Gohring G, Giagounidis A, Busche G, Hofmann W, Kreipe HH, Fenaux P, Hellstrom-Lindberg E, Schlegelberger B (2011) Cytogenetic follow-up by karyotyping and fluorescence in situ hybridization: implications for monitoring patients with myelodysplastic syndrome and deletion 5q treated with lenalidomide. Haematologica 96(2):319–322

Grisendi S, Bernardi R, Rossi M, Cheng K, Khandker L, Manova K, Pandolfi PP (2005) Role of nucleophosmin in embryonic development and tumorigenesis. Nature 437(7055):147–153

Horrigan SK, Arbieva ZH, Xie HY, Kravarusic J, Fulton NC, Naik H, Le TT, Westbrook CA (2000) Delineation of a minimal interval and identification of 9 candidates for a tumor suppressor gene in malignant myeloid disorders on 5q31. Blood 95(7):2372–2377

Jadersten M, Karsan A (2011) Clonal evolution in myelodysplastic syndromes with isolated del(5q): the importance of genetic monitoring. Haematologica 96(2):177–180

Jadersten M, Saft L, Smith A, Kulasekararaj A, Pomplun S, Gohring G, Hedlund A, Hast R, Schlegelberger B, Porwit A, Hellstrom-Lindberg E, Mufti GJ (2011) TP53 mutations in low-risk myelodysplastic syndromes with del(5q) predict disease progression. J Clin Oncol 29(15):1971–1979

Jaffe E, Harris HN, Stein H et al (eds) (2001) WHO classification of tumours: pathology and genetics of haematopoietic and lymphoid tissues. IARC Press, Lyon

Jaju RJ, Jones M, Boultwood J, Kelly S, Mason DY, Wainscoat JS, Kearney L (2000) Combined immunophenotyping and FISH identifies the involvement of B-cells in 5q− syndrome. Genes Chromosomes Cancer 29(3):276–280

Joslin JM, Fernald AA, Tennant TR, Davis EM, Kogan SC, Anastasi J, Crispino JD, Le Beau MM (2007) Haploinsufficiency of EGR1, a candidate gene in the del(5q), leads to the development of myeloid disorders. Blood 110(2):719–726

Kiladjian JJ, Bourgeois E, Lobe I, Braun T, Visentin G, Bourhis JH, Fenaux P, Chouaib S, Caignard A (2006) Cytolytic function and survival of natural killer cells are severely altered in myelodysplastic syndromes. Leukemia 20(3):463–470

Kumar MS, Narla A, Nonami A, Mullally A, Dimitrova N, Ball B, McAuley JR, Poveromo L, Kutok JL, Galili N, Raza A, Attar E, Gilliland DG, Jacks T, Ebert BL (2011) Coordinate loss of a microRNA and protein-coding gene cooperate in the pathogenesis of 5q− syndrome. Blood 118(17):4666–4673

La Starza R, Matteucci C, Gorello P, Brandimarte L, Pierini V, Crescenzi B, Nofrini V, Rosati R, Gottardi E, Saglio G, Santucci A, Berchicci L, Arcioni F, Falini B, Martelli MF, Sambani C, Aventin A, Mecucci C (2010) NPM1 deletion is associated with gross chromosomal rearrangements in leukemia. PLoS One 5(9):e12855

Lane SW, Sykes SM, Al-Shahrour F, Shterental S, Paktinat M, Lo Celso C, Jesneck JL, Ebert BL, Williams DA, Gilliland DG (2010) The Apc(min) mouse has altered hematopoietic stem cell function and provides a model for MPD/MDS. Blood 115(17):3489–3497

List A, Dewald G, Bennett J, Giagounidis A, Raza A, Feldman E, Powell B, Greenberg P, Thomas D, Stone R, Reeder C, Wride K, Patin J, Schmidt M, Zeldis J, Knight R (2006) Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med 355(14):1456–1465

Liu TX, Becker MW, Jelinek J, Wu WS, Deng M, Mikhalkevich N, Hsu K, Bloomfield CD, Stone RM, DeAngelo DJ, Galinsky IA, Issa JP, Clarke MF, Look AT (2007) Chromosome 5q deletion and epigenetic

suppression of the gene encoding alpha-catenin (CTNNA1) in myeloid cell transformation. Nat Med 13(1):78–83

Lopez-Villar O, Garcia JL, Sanchez-Guijo FM, Robledo C, Villaron EM, Hernandez-Campo P, Lopez-Holgado N, Diez-Campelo M, Barbado MV, Perez-Simon JA, Hernandez-Rivas JM, San-Miguel JF, del Canizo MC (2009) Both expanded and uncultured mesenchymal stem cells from MDS patients are genomically abnormal, showing a specific genetic profile for the 5q− syndrome. Leukemia 23(4):664–672

Mallo M, Cervera J, Schanz J, Such E, Garcia-Manero G, Luno E, Steidl C, Espinet B, Vallespi T, Germing U, Blum S, Ohyashiki K, Grau J, Pfeilstocker M, Hernandez JM, Noesslinger T, Giagounidis A, Aul C, Calasanz MJ, Martin ML, Valent P, Collado R, Haferlach C, Fonatsch C, Lubbert M, Stauder R, Hildebrandt B, Krieger O, Pedro C, Arenillas L, Sanz MA, Valencia A, Florensa L, Sanz GF, Haase D, Sole F (2011) Impact of adjunct cytogenetic abnormalities for prognostic stratification in patients with myelodysplastic syndrome and deletion 5q. Leukemia 25(1):110–120

Narla A, Ebert BL (2010) Ribosomopathies: human disorders of ribosome dysfunction. Blood 115(16):3196–3205

Nilsson L, Astrand-Grundstrom I, Arvidsson I, Jacobsson B, Hellstrom-Lindberg E, Hast R, Jacobsen SE (2000) Isolation and characterization of hematopoietic progenitor/stem cells in 5q-deleted myelodysplastic syndromes: evidence for involvement at the hematopoietic stem cell level. Blood 96(6):2012–2021

Nilsson L, Eden P, Olsson E, Mansson R, Astrand-Grundstrom I, Strombeck B, Theilgaard-Monch K, Anderson K, Hast R, Hellstrom-Lindberg E, Samuelsson J, Bergh G, Nerlov C, Johansson B, Sigvardsson M, Borg A, Jacobsen SE (2007) The molecular signature of MDS stem cells supports a stem-cell origin of 5q myelodysplastic syndromes. Blood 110(8):3005–3014

Padua RA, Guinn BA, Al-Sabah AI, Smith M, Taylor C, Pettersson T, Ridge S, Carter G, White D, Oscier D, Chevret S, West R (1998) RAS, FMS and p53 mutations and poor clinical outcome in myelodysplasias: a 10-year follow-up. Leukemia 12(6):887–892

Pedersen-Bjergaard J, Andersen MK, Andersen MT, Christiansen DH (2008) Genetics of therapy-related myelodysplasia and acute myeloid leukemia. Leukemia 22(2):240–248

Pellagatti A, Jadersten M, Forsblom AM, Cattan H, Christensson B, Emanuelsson EK, Merup M, Nilsson L, Samuelsson J, Sander B, Wainscoat JS, Boultwood J, Hellstrom-Lindberg E (2007) Lenalidomide inhibits the malignant clone and up-regulates the SPARC gene mapping to the commonly deleted region in 5q− syndrome patients. Proc Natl Acad Sci U S A 104(27):11406–11411

Pellagatti A, Hellstrom-Lindberg E, Giagounidis A, Perry J, Malcovati L, Della Porta MG, Jadersten M, Killick S, Fidler C, Cazzola M, Wainscoat JS, Boultwood J (2008) Haploinsufficiency of RPS14 in 5q− syndrome is associated with deregulation of ribosomal- and translation-related genes. Br J Haematol 142(1):57–64

Pellagatti A, Cazzola M, Giagounidis A, Perry J, Malcovati L, Della Porta MG, Jadersten M, Killick S, Vyas P, Hellstrom-Lindberg E, Wainscoat JS, Boultwood J (2011) Marked down-regulation of nucleophosmin-1 is associated with advanced del(5q) myelodysplastic syndrome. Br J Haematol 155(2):272–274

Ramakrishnan A, Awaya N, Bryant E, Torok-Storb B (2006) The stromal component of the marrow microenvironment is not derived from the malignant clone in MDS. Blood 108(2):772–773

Soenen-Cornu V, Tourino C, Bonnet ML, Guillier M, Flamant S, Kotb R, Bernheim A, Bourhis JH, Preudhomme C, Fenaux P, Turhan AG (2005) Mesenchymal cells generated from patients with myelodysplastic syndromes are devoid of chromosomal clonal markers and support short- and long-term hematopoiesis in vitro. Oncogene 24(15):2441–2448

Sportoletti P, Grisendi S, Majid SM, Cheng K, Clohessy JG, Viale A, Teruya-Feldstein J, Pandolfi PP (2008) Npm1 is a haploinsufficient suppressor of myeloid and lymphoid malignancies in the mouse. Blood 111(7):3859–3862

Starczynowski DT, Kuchenbauer F, Argiropoulos B, Sung S, Morin R, Muranyi A, Hirst M, Hogge D, Marra M, Wells RA, Buckstein R, Lam W, Humphries RK, Karsan A (2010) Identification of miR-145 and miR-146a as mediators of the 5q− syndrome phenotype. Nat Med 16(1):49–58

Starczynowski DT, Morin R, McPherson A, Lam J, Chari R, Wegrzyn J, Kuchenbauer F, Hirst M, Tohyama K, Humphries RK, Lam WL, Marra M, Karsan A (2011) Genome-wide identification of human microRNAs located in leukemia-associated genomic alterations. Blood 117(2):595–607

Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J (2008) WHO classification of tumours of haematopoietic and lymphoid tissues. IARC Press, Lyon

Tehranchi R, Woll PS, Anderson K, Buza-Vidas N, Mizukami T, Mead AJ, Astrand-Grundstrom I, Strombeck B, Horvat A, Ferry H, Dhanda RS, Hast R, Ryden T, Vyas P, Gohring G, Schlegelberger B, Johansson B, Hellstrom-Lindberg E, List A, Nilsson L, Jacobsen SE (2010) Persistent malignant stem cells in del(5q) myelodysplasia in remission. N Engl J Med 363(11):1025–1037

Van den Berghe H, Cassiman JJ, David G, Fryns JP, Michaux JL, Sokal G (1974) Distinct haematological disorder with deletion of long arm of no. 5 chromosome. Nature 251(5474):437–438

Venner CP, List AF, Neville TJ, Deeg HJ, Caceres G, Scott BL, Sokol L, Sung S, Karsan A (2010) Induction of micro RNA-143 and 145 in pre-treatment CD34+ cells from patients with myelodysplastic syndrome (MDS) after in vitro exposure to lenalidomide correlates with clinical response in patients harboring the del5q abnormality. Blood 116(21 Suppl):A123 Suppl

Wang J, Fernald AA, Anastasi J, Le Beau MM, Qian Z (2010) Haploinsufficiency of Apc leads to ineffective hematopoiesis. Blood 115(17):3481–3488

Wei S, Chen X, Rocha K, Epling-Burnette PK, Djeu JY, Liu Q, Byrd J, Sokol L, Lawrence N, Pireddu R, Dewald G, Williams A, Maciejewski J, List A (2009) A critical role for phosphatase haplodeficiency in the selective suppression of deletion 5q MDS by lenalidomide. Proc Natl Acad Sci U S A 106(31): 12974–12979

Ximeri M, Galanopoulos A, Klaus M, Parcharidou A, Giannikou K, Psyllaki M, Symeonidis A, Pappa V, Kartasis Z, Liapi D, Hatzimichael E, Kokoris S, Korkolopoulou P, Sambani C, Pontikoglou C, Papadaki HA (2010) Effect of lenalidomide therapy on hematopoiesis of patients with myelodysplastic syndrome associated with chromosome 5q deletion. Haematologica 95(3):406–414

Zhao N, Stoffel A, Wang PW, Eisenbart JD, Espinosa R 3rd, Larson RA, Le Beau MM (1997) Molecular delineation of the smallest commonly deleted region of chromosome 5 in malignant myeloid diseases to 1–1.5 Mb and preparation of a PAC-based physical map. Proc Natl Acad Sci U S A 94(13):6948–6953