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Chapter

Introductory Chapter: Progress in Myelodysplastic Syndrome Area

Ota Fuchs

1. Advances in our knowledge of cytogenetic abnormalities and gene mutations

Myelodysplastic syndromes (MDS) constitute a group of age-associated heterogeneous clonal hematopoietic disorders characterized by ineffective hematopoiesis with peripheral cytopenias, dysplasia, and an increased risk of progression to acute myeloid leukemia (AML) [1–6]. About 50% of cases of MDS are characterized by the presence of cytogenetic abnormalities. Losses of chromosomal material as del(5q), del(20q), monosomy 7 or del(7q), and del(Y) are most common cytogenetic abnormalities and are more frequent than gains of chromosomal material as trisomy 8 or trisomy 21 [7].

MDS are caused by abnormalities in many genes. The great progress in analysis of these mutations and in elucidation of relationships between gene mutations and clinical phenotypes of these disorders was achieved. Somatic mutations were found in more than 90%. Next-generation sequencing (NGS) detected about 10 different mutations in almost every patient with MDS. The majority of these mutations are nonpathogenic passenger mutations. However, one or more driver mutations in most patients with MDS are associated with the pathogenesis of MDS. Gene mutations affect proteins involved in various important cell processes as RNA-splicing, DNA methylation, histone and chromatin modifications, signal transduction, transcription (transcription factors), tumor suppressor (*TP53*), *RAS* pathway, and separation of sister chromatids during cell division (cohesion complex) [4, 8–10].

RNA-splicing and DNA methylation mutations occur early and are known as founding mutations. Other mutations are called subclonal mutations. No MDS-specific mutations exist. Strongly represented mutations in genes coding for proteins involved in DNA methylation, such as *TET2*, *DNMT3A*, and *ASXL1*, are common also in older individuals with normal blood count (clonal hematopoiesis of indeterminate potential/CHIP/) [11, 12]. Until now, mutations in *TP53*, *EZH2*, *RUNX1*, and *SF3B1* predict independently overall survival (OS) of MDS patients. The first three mutations are associated with shorter OS but the last mutation is connected with better survival in refractory anemia with ring sideroblast (MDS-RS) and with thrombocytosis (RARS-T) [13, 14]. *SF3B1* mutations are present in about 80% of MDS-RS and correlates with its development. *SF3B1* mutations could alter the expression of the gene for ABCB7 transporter and abnormally regulate iron homeostasis in mitochondria mediating the phenotype of acquired MDS-RS [15]. Effects of other mutations are not clear up to now and results are often controversial.

We lack clinical methods to stop clonal development from relatively benign state of CHIP to malignancy. Especially, *TP53*-mutant clones induce progress to therapy-related MDS/AML. Therapy-related myeloid neoplasms have mutations in *TP53* and

epigenetic modifying genes, instead of mutations in tyrosine kinase and spliceosome genes [16]. The possible treatments are now the use of hypomethylating agents or in future anti-inflammatory therapy and clonally selective immunotherapies.

MDS are associated with genomic instability and extensive DNA damage caused by deficient repair mechanisms. Aberrations in DNA damage response/repair genes other than *TP53* and some genes involved in DNA damage checkpoints are rare. Differential expression of homologous recombination DNA repair-associated genes during MDS progression was detected and could be confirmed as new biomarkers related to pathogenesis and poor prognosis in MDS [17, 18].

2. Advance in our understanding of del(5q) myelodysplastic syndrome pathogenesis and its treatment with lenalidomide

The greatest progress was achieved in the study of molecular pathogenesis of del(5q) MDS disease phenotype and its treatment by immunomodulatory or cereblon-binding drug lenalidomide [2, 19–35]. Ebert et al. described that impaired ribosome biosynthesis due to *RPS14* (ribosomal protein 14 of the small ribosome subunit) gene haploinsufficiency leads to the E3 ubiquitin ligase HDM2 (human homolog to mouse double minute 2, major negative regulator of p53) inactivation by free ribosomal proteins, particularly RPL11 [36]. HDM2 degradation drives p53-mediated apoptosis of erythroid cells carrying the del(5q) aberration. This p53-mediated apoptosis of erythroid cells is a key effector of hypoplastic anemia in MDS patients with del(5q) [36]. *RPS14* haploinsufficiency causes a block in erythroid differentiation mediated by calprotectin (the heterodimeric S100 calcium-binding proteins S100A8 and S100A9) [37]. Proinflammatory proteins, S100A9 and tumor necrosis factor-α, suppress the effect of erythropoietin in MDS [38]. Some patients originally considered as MDS patients without del(5q) can have a phenotype of atypical 5q− syndrome and can be sensitive to lenalidomide therapy because they have diminutive somatic deletions in the 5q region. These deletions were not identified by fluorescence in situ hybridization or cytogenetic testing but by single nucleotide polymorphism array genotyping [39]. Low RPS14 expression in 50–70% MDS patients without del(5q) confers higher apoptosis rate of nucleated erythrocytes and predicts prolonged survival [40, 41].

What is the mechanism of lenalidomide in del(5q) MDS based on what has been achieved and elucidated to date? Lenalidomide stabilizes E3 ubiquitin ligase HDM2, thereby accelerating p53 degradation [42, 43]. Lenalidomide inhibits phosphatases PP2a and Cdc25c (coregulators of cell cycle which genes are very commonly deleted in del(5q) MDS) with consequent G2 arrest of del(5q) MDS progenitors and their apoptosis. PP2a and Cdc25c inhibition by lenalidomide suppress HDM2 autoubiquitination and subsequent degradation. Thus, lenalidomide has been shown to not only reverse apoptosis within the erythroid compartment, but also directly induce apoptosis of the myeloid clone in del(5q) MDS [44, 45]. Lenalidomide upregulates expression of other two haploinsufficient genes located on chromosome 5q, genes for microRNAs (miR-145 and miR-146a) [46]. These miRs are involved in Toll-like receptor pathway, IL-6 induction, and regulation of megakaryopoiesis [20].

Ito et al. discovered that thalidomide (founding member of immunomodulatory drugs/IMiDs/) binds cereblon (CRBN) in the terminal C-region (parts of exons 10 and 11 of the *CRBN* gene code this IMiD binding region) [47]. Several researchers confirmed CRBN as target of lenalidomide in multiple myeloma (MM), lymphoma, chronic lymphocytic leukemia, and del(5q) MDS [48]. CRBN is the ubiquitously expressed 51 kDa protein with a putative role in cerebral development, especially memory and learning [49, 50].

Our group found that del(5q) MDS patients (the so-called 5q minus syndrome) have higher levels of full-length CRBN mRNA than other patients with lower risk MDS, linking higher levels of a known lenalidomide target CRBN and del(5q) MDS subgroup known to be especially sensitive to lenalidomide [51].

CRBN is a member and substrate receptor of the cullin 4 RING E3 ubiquitin ligase complex (CRL4). CRBN recruits substrate proteins to the CRL4 complex for ubiquitination and the subsequent degradation in proteasomes. IMiDs binds to CRBN in CRL4 complex and block normal endogenous substrates (CRBN and the homeobox transcription factor MEIS2 in multiple myeloma/MM/) from binding to CRL4 for ubiquitination and degradation [52]. After IMID binding to CRBN, CRL4 complex is recruiting transcription factors Ikaros (IKZF1) and Aiolos (IKZF3) for ubiquitination and degradation in MM cells [53]. Degradation of these transcription factors explains lenalidomide's growth inhibition of MM cells and increased interleukin-2 (IL-2) release from T cells. However, it is unlikely that degradation of IKZF1 and IKZF3 accounts for lenalidomide's activity in MDS with del(5q). Fink et al. identified a novel target casein kinase1A1 (CSNK1A1) by quantitative proteomics in the myeloid cell line KG-1 [54]. CSNK1A1 is encoded in the del(5q) commonly deleted region and the gene is haploinsufficient. Lenalidomide treatment leads to increased ubiquitination of the remaining CSNK1A1 and decreased protein abundance. CSNK1A1 negatively regulates β-catenin which drives stem cell self-renewal, and *CSNK1A1* haploinsufficiency causes the initial clonal expansion in patients with the del(5q) MDS and contributes to the pathogenesis of del(5q) MDS. The further inhibition of CSNK1A1 in del(5q) MDS is associated with del(5q) failure and p53 activation. The inhibition of CSNK1A1 reduced RPS6 phosphorylation, induced p53 expression and growth inhibition, and triggered myeloid differentiation program. TP53-null leukemia did not respond to CSNK1A1 inhibition, strongly supporting the importance of the p53 expression for the yield of CSNK1A1 inhibition. *CSNK1A1* mutations have been recently found in 5–18% of MDS patients with del(5q) [55]. These mutations are associated similarly to the effect of *TP53* mutations with rise to a poor prognosis in del(5q) MDS [56]. Other studies did not find impact of *CSNK1A1* mutations on lenalidomide treatment in del(5q) MDS [57, 58].

Even if the treatment of del(5q) MDS patients with lenalidomide is very efficient, 50% of treated patients relapse after 2–3 years. Martinez-Hoyer et al. found that low platelet count and occurrence of additional mutations, mainly *TP53* mutations induce lenalidomide resistance [59–61]. They used whole genome sequencing and observed in several resistant patients mutations in *RUNX1* gene or decreased amount of *RUNX1* transcript without aberration in *TP53* [59]. Results were verified in model system of two human del(5q) lines, MDS-L and KG-1a. *RUNX1* knock-out or RUNX1 shRNA increased proliferation and reduced apoptosis in lenalidomide-treated cells with decreased *RUNX1* transcript. Therefore, effect of lenalidomide in del(5q) requires functional RUNX1. Similar results were obtained with *TP53* knock-out cells. Both *RUNX1* and *TP53* transcripts cooperate and alter the activity of GATA2 transcriptional complex [59].

3. Studies on lenalidomide use also in lower risk non-del(5q) MDS treatment and new possible therapies

While CSNK1A1 is $CRL4^{CRBN}$ target in del(5q) MDS, $CRL4^{CRBN}$ targets in lower risk non-del(5q) remain to be determined. The mechanism of action of lenalidomide is still unclear in non-del(5q) MDS cells. Recent evidence shows that lenalidomide directly improves erythropoietin receptor (EPOR) signaling by EPOR upregulation mediated by a posttranscriptional mechanism [62]. Lenalidomide

stabilizes the EPOR protein by inhibition of the E3 ubiquitin ligase RNF41 (ring finger protein 41, also known as neuregulin receptor degradation protein-1/Nrdp1/ and fetal liver ring finger/FLRF/) responsible for EPOR polyubiquitination and next degradation [62] and induces lipid raft assembly to enhance EPOR signaling in MDS erythroid progenitors [63, 64].

After failure of ESAs, lenalidomide yields red blood cell transfusion independence in 20–30% of lower risk non-del(5q) MDS. Indeed, several observations suggest an additive effect of ESA and lenalidomide in this situation [65, 66] and also in del(5q) MDS patients [67]. Synthetic corticosteroids (dexamethasone and prednisone) are also able to potentiate the effect of lenalidomide or combination of lenalidomide and erythropoietin [67–69].

Basiorka et al. and Sallman et al. reported activation of the NLRP3 inflammasome in MDS [70, 71]. NRLP3 drives clonal expansion and pyroptotic cell death. Independent of genotype, MDS hematopoietic stem and progenitor cells (HSPCs) overexpress inflammasome proteins. Activated NLRP3 complexes direct then activation of caspase-1, generation of interleukin-1β (IL-1β) and IL-18, and pyroptotic cell death. Mechanistically, pyroptosis is triggered by the alarmin S100A9 that is found in excess in MDS HSPCs and bone marrow plasma. Further, like somatic gene mutations, S100A9-induced signaling activates NADPH oxidase (NOX) and increasing levels of reactive oxygen species (ROS). ROS initiate cation influx, cell swelling, and β-catenin activation. Knockdown of NLRP3 or caspase-1, neutralization of S100A9, and pharmacologic inhibition of NLRP3 or NOX suppress pyroptosis, ROS generation, and nuclear β-catenin in MDSs and are sufficient to restore effective hematopoiesis. Thus, alarmins and founder gene mutations in MDSs cause a common redox-sensitive inflammasome circuit. They are new candidates for therapeutic intervention.

Not only apoptosis and pyroptosis are involved in increased cell death in MDS. Recently, possible further mechanism of cell death, necroptosis, in MDS has been described [72, 73]. Necroptosis is like pyroptosis associated with membrane permeabilization and the release of damage-associated molecular patterns (DAMPs) such as alarmins. Alarmins bind Toll-like receptor 4 (TLR4) and activate the transcription factor NF-κB and inflammation [74].

The effects of lenalidomide in non-del(5q) are thought to be secondary to modulation of the immune system. Hyperactivated T cells inhibit hematopoiesis. Immunosuppressive therapies with antithymocyte globulin alone and in combination with prednisone or cyclosporine show response rates between 25 and 40% [75, 76].

The studies discussed in this and other chapters of this book will help to translate our knowledge of genetic aberrations and of pathophysiological mechanisms in MDS into clinical use in diagnosis, prognosis, and therapy. Novel agents developed on the basis of this knowledge (luspatercept, rigosertib, immune checkpoint inhibitors, venetoclax, and others) are in clinical trials and will help in relapsed/refractory MDS.

The work of our group in this area was supported by the research project for conceptual development of research organization (00023736; Institute of Hematology and Blood Transfusion, Prague) from the Ministry of Health of the Czech Republic.

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