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636.MYELODYSPLASTIC SYNDROMES-BASIC AND TRANSLATIONAL

Interactions between Iron Overload, Oxidative Stress, and Somatic Mutations in Myelodysplastic Syndromes; Evidence from the Literature

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Introduction: Somatic mutations (SM) are central to the pathophysiology of myelodyspastic syndromes (MDS). Iron overload (IOL) from transfusion of red blood cells (RBC) and the oxidative stress that results from the ability of iron to transfer electrons and undergo Fenton chemistry are common and are associated with adverse clinical endpoints (infections, cardiac events, exacerbation of bone marrow failure, event-free survival, progression-free survival, overall survival) in MDS. We reviewed the literature to elucidate what evidence is available indicating an interaction between iron, oxidative stress and specific SM in MDS.

Methods: A series of PubMed searches were done including the key words of each specific mutation combined with iron, oxidative stress, and reactive oxygen species (ROS, a measure of oxidative stress), focusing on SM prevalent in MDS and/or included in the molecular International Prognostic Scoring System (IPSS-M; 31 mutations in all, including IPSS-M mutations and TET2). Citations relevant to hematopoietic stem and progenitor cells, cells of the hematopoietic microenvironment, and myeloid disorders were favoured for review. Mutations of familial predisposing conditions were also searched in combination with iron, oxidative stress and ROS.

Results: Of 31 mutations found in the IPSS-M, an additional four mutations found in familial predisposing conditions (DDX41, GATA2, CHEK2, SAMD9) were searched as was TET2, for a total of 35 mutations. Fifty-four references were identified. Fifty-three references were preclinical/translational in nature, with one case report (WT1). The most frequent alterations in iron/ROS were with the SF3B1 mutation, with 11 citations. Thirteen of 31 (42%) of SM in combination with iron, oxidative stress/ROS had citations. Reports for combination with iron or oxidative stress/ROS, respectively, included early (TP53, IDH2, RUNX1, SF3B1, STAG2, TET2; and TP53, DNMT3A, IDH2, NPM1, U2AF1) and late (NRAS, CEBP3A; and CBL, NRAS) mutations. Both gain of function (TP53, IDH2, NRAS, SF3B1; and TP53, IDH2, NRAS, U2AF1) and loss of function (STAG2, TET2; and CBL) mutations had relevant citations identified. Cellular pathways affected included tumour suppressor (TP53 for both iron and oxidative stress/ROS), signal transduction (NRAS for both), splicing factors (SF3B1; U2AF1), DNA stability (STAG2) and (hypo) methylation (TET2; DNMT3A). There were reports of an impact at multiple levels on iron/ROS and cellular/systemic physiology in the context of SF3B1 mutation, for example: ERFE+12 (containing 12 additional nucleotides and translated to an ERFE protein containing 4 additional amino acids; 358 vs 354 in wild type) present in SF3B1 mutated MDS does like the usual ERFE suppress hepcidin, impacting iron at a systemic level; enzymes of iron, heme and iron sulfur cluster physiology are altered, impacting iron physiology at a cellular level; and mitochondrial ferritin sequesters iron, leading to cytoplasmic iron deficiency, lowering ROS and thus possibly protecting cells from oxidative damage. Table 1 shows examples of iron/ROS interactions with SF3B1, TET2, DNMT3A, U2AF1, STAG2, NRAS, TP53, IDH2, CBL, NPM, ETNK, PTPN11, WT1 and RUNX1. Figure 1 shows MDS pathophysiology and where interactions between SM and iron/oxidative stress/ROS may impact this pathophysiology. No investigations were identified relevant to the mutations of familial predisposing conditions, including DDX41, GATA2, CHEK2 and SAMD9 in combination with iron/oxidative stress/ROS.

Discussion: Searching IOL, oxidative stress and ROS in combination with MDS somatic mutations uncovered information as to how iron/redox status may interact with SM to affect MDS pathophysiology. Of particular interest is the cytoplasmic iron deficiency induced in the presence of SF3B1 mutation, the only SM conferring favourable prognosis in MDS in the IPSS-M. Given the pleiotropic cellular, intracellular and subcellular mechanisms involved, investigation regarding when and how targeting iron overload by reducing RBC transfusion requirements, binding iron or attenuating ROS may alter cellular and clinical outcomes in the setting of specific somatic mutations is warranted.

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Table 1. Iron, oxidative stress/ROS & specific SM prevalent in MDS [1, 2].

SM	#Refs	%[3]	Function	Early /late[3]	GOF/ LOF	Prog[3]	Study type	Findings	reference
SF3B1	11	24	RNA splicing	E	GOF	F[4]	Preclinical	Alteration in cellular and body iron status	Dolatshad 2015, 2016; Ye 2010; Liu 2020; Crooks 2010; Clough 2022; Conte 2015; Shiozawa 2018; Arribagllo 2013; Bondu 2019
TET2	3	30	DNA demethylation	E	LOF	N	Preclinical	Decrease alters cellular iron physiology. Iron a TET2 cofactor	Inokura 2017; Huang 2020; Qu 2018
DNMT3A	4	26	DNA methylation	E	LOF	U	Preclinical	ROS implicated in AML progression	Bera 2018; Maltseva 2009; Jung 2020
U2AF1	2	8	RNA splicing	E	GOF/LOF	U	Preclinical	Increases ROS	Liu 2021; Goncalves 2021
STAG2	1	8	DNA replication	L	LOF	U	Preclinical	Loss alters cellular iron balance	Bailey 2021
NRAS	4	4	Signal transduction	L	GOF	U	Preclinical	Alters autophagy, cell death, redox status, oxidative DNA lesions	Bartolacci 2021; Ney 2021; Kopnin 2007; Rassool 2007
TP53[5]	4	11	Tumour suppressor	E	GOF	U[6]	Preclinical	Alters iron homeostasis, cellular redox status	Calabrese 2020; Smith-Diaz 2021; Li 2021; Sallman 2021
IDH2	3	4	DNA methylation	L	GOF	U	Preclinical	Iron & ROS involved in AML progression	Chen 2016; Testa 2020; Kingsbury 2016
CBL	1	4	E3 ubiquitin ligase	E	LOF	U	In-direct	Defective ROS downregulation	Nakata 2017
NPM	5	1	Stress response	E	LOF	U	Preclinical/ In-direct	NPM unable to shuttle to nucleus & activate stress response	Liu 2017
ETNK	1	2	Membrane lipid PE synthesis	?	LOF	U	preclinical	Increases ROS	Fontana 2020
PTPN11	3	2	Tyrosine phosphatase	L	GOF	U	preclinial	Cytokine & kinase activation, cell senescence via cysteine oxidation	Xu 2013; Zheng 2013; Meng 2002
WT1	1	2	Interacts with TET2	E?	LOF	U	Case report	?loses ability to modulate methylation via ROS?	Shimizu 2016
RUNX1	2	11	Nuclear transcription factor	E	LOF	U	In-direct	Inhibits cell differentiation via HIF1a Fe effect?	Siegert 2015; Movafagh 2015

[1]No references were identified on iron, oxidative stress or ROS in the context of ASXL1, BCOR, BCORL1, CEBPA, ETV6, EZH2, FLT3, GATA2, GNB1, IDH1, KLL, NF1, PHF6, PPM1D, PRPF8, RUNX1 (indirect evidence), SETBP1, SRSF2, ZRSR2. [2]Papaemmanuil E, et. Al. 2013 Blood 122:3616. [3]Bernard E, et al. NEJM Evidence. 2022;1(7). [4]Modulated by pattern of comutations". [5]TP53 multi-hit mutations". [6]Abbreviations: E, early; F, favourable, Fe, iron; GOF, gain of function; L, late; LOF, loss of function; N, neutral; PE, phosphatidylethanolamine; Pre, preclinical; Prog, prognostic implications; ROS, reactive oxygen species; U, unfavourable..

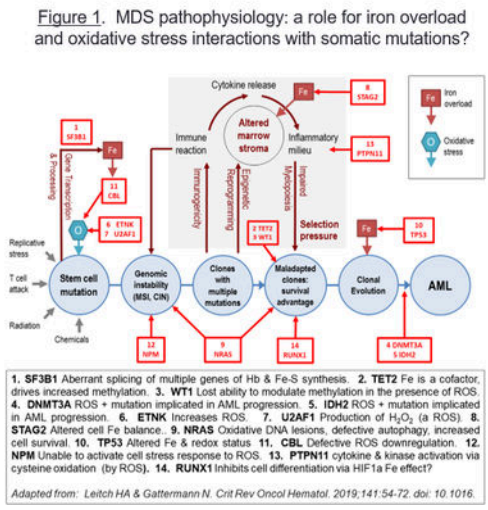

Figure 1

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