Advances in Experimental Medicine and Biology 1326
Cell Biology and Translational Medicine

Kursad Turksen *Editor*

Cell Biology and Translational Medicine, Volume 12

Stem Cells in Development and Disease

Springer

Advances in Experimental Medicine and Biology

Cell Biology and Translational Medicine

Volume 1326

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Editor

Cell Biology and Translational Medicine, Volume 12

Stem Cells in Development and Disease

Springer

Editor
Kursad Turksen *(emeritus)*
Ottawa Hospital Research Institute
Ottawa, ON, Canada

ISSN 0065-2598 ISSN 2214-8019 (electronic)
Advances in Experimental Medicine and Biology
ISSN 2522-090X ISSN 2522-0918 (electronic)
Cell Biology and Translational Medicine
ISBN 978-3-030-71932-6 ISBN 978-3-030-71933-3 (eBook)
https://doi.org/10.1007/978-3-030-71933-3

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

This next volume in the Cell Biology and Translational Medicine series addresses the topic of stem cells in development and diseases. Amongst specialized topics, there are chapters on the role of stem cells neuronal development and the role of stem cells in diseases including arthritis, aging and cancer.

I remain very grateful to Gonzalo Cordova, associate editor of the series, and acknowledge his continuous support.

I would also like to acknowledge and thank Mariska van der Stigchel, assistant editor, for her outstanding efforts in helping to get this volume to the production stages.

A special thank you goes to Shanthi Ramamoorthy and Rathika Ramkumar for their outstanding efforts in the production of this volume.

Finally, sincere thanks to the contributors not only for their support of the series, but also for their insights and efforts to capture both the advances and the remaining obstacles in their areas of research. I trust readers will find their contributions as interesting and helpful as I have.

Ottawa, ON, Canada — Kursad Turksen

Contents

Adv Exp Med Biol - Cell Biology and Translational Medicine (2021) 12: 1–10
https://doi.org/10.1007/5584_2020_608

Published online: 1 January 2021

Immune Dysregulation and Recurring Mutations in Myelodysplastic Syndromes Pathogenesis

Anacélia Matos, Silvia M. M. Magalhães, and Michael J. Rauh

Abstract

Myelodysplastic syndromes (MDS) are clonal stem cell malignancies characterized by ineffective hematopoiesis leading to peripheral cytopenias and variable risk of progression to acute myeloid leukemia. Inflammation is associated with MDS pathogenesis. Several cytokines, reactive species of oxygen/nitrogen and growth factors are directly or indirectly involved in dysfunction of the MDS bone marrow (BM) microenvironment. Mutations in genes mainly regulating RNA splicing, DNA methylation and chromatin accessibility, transcription factors, signal transduction and the response to DNA damage contribute to ineffective hematopoiesis, genomic instability and MDS development. The inflammation-associated DNA damage in hematopoietic stem cells may also contribute to MDS development and progression with aggressive clinical characteristics. Many studies have aimed at clarifying mechanisms involved in the activity of immature myeloid cells as powerful modulators of the immune response and their correlation with aging, autoimmunity, and development of cancer. In this review, we explore recent advances and accumulating evidence uniting immune dysregulation, inflammaging and recurring mutations in the pathogenesis of MDS.

Keywords

Bone marrow · Hematopoietic stem cells · Inflammation · Mutations · Myelodysplastic syndromes

Authors Silvia M. M. Magalhães and Michael J. Rauh have equally contributed to this chapter.

A. Matos
Cancer Cytogenomic Laboratory, Federal University of Ceará, Fortaleza, Brazil

Post-graduate Program in Medical Science, Federal University of Ceará, Fortaleza, Brazil

S. M. M. Magalhães
Cancer Cytogenomic Laboratory, Federal University of Ceará, Fortaleza, Brazil

Post-graduate Program in Medical Science, Federal University of Ceará, Fortaleza, Brazil

Department of Clinical Medicine, Federal University of Ceará, Fortaleza, Brazil
e-mail: silviamm@ufc.br

M. J. Rauh (✉)
Department of Pathology and Molecular Medicine, Queen's University, Kingston, ON, Canada
e-mail: michael.rauh@queensu.ca; rauhm@queensu.ca

Abbreviations

AML	acute myeloid leukemia
ARG1	arginase 1
ASXL1	Additional Sex Combs Like 1, Transcriptional Regulator
BM	bone marrow

CBL	Casitas B-Lineage Lymphoma Proto-Oncogene
CCUS	clonal cytopenia of undetermined significance
CD	cluster of differentiation
CHIP	clonal hematopoiesis of indeterminate potential
CSF	colony-stimulating factor
DAMP	danger-associated molecular pattern
del	deletion
DNA	deoxyribonucleic acid
DNMT3A	DNA methyltransferase 3A
eMDSC	early MDSC
ETV6	ETS Variant Transcription Factor 6
EZH2	Enhancer Of Zeste 2 Polycomb Repressive Complex 2 Subunit
G	granulocytic
GATA2	GATA Binding Protein 2
GM	granulocyte-monocyte
HLA	human leukocyte antigen
HSPC	hematopoietic stem/progenitor cell
IDH1/2	isocitrate dehydrogenases 1 and 2
IFN-γ	interferon gamma
IL	interleukin
IMC	immature myeloid cell
iNOS	inducible nitric oxide synthase
IPSS	International prognostic scoring system
JAK2	Janus Kinase 2
L-Arg	L-arginine
M	monocytic
MDS	myelodysplastic syndromes
MDSC	myeloid-derived suppressor cell
miR	micro RNA
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NK	natural killer
NKT	natural killer/T
NO	nitric oxide
NRAS	Neuroblastoma RAS Viral (V-Ras) Oncogene Homolog
PAMP	pathogen-associated molecular pattern
PGE2	prostaglandin E2
PMN	polymorphonuclear
PPM1D	Protein Phosphatase, Mg2+/Mn2+ Dependent 1D
RAD21	RAD21 Cohesin Complex Component
RNA	ribonucleic acid
ROS	reactive oxygen species
RUNX1	RUNX Family Transcription Factor 1
S100A8	S100 Calcium Binding Protein A8
S100A9	S100 Calcium Binding Protein A9
SF3B1	Splicing Factor 3b Subunit 1
SRSF2	Serine And Arginine Rich Splicing Factor 2
STAG2	Stromal Antigen 2
TAM	tumour-associated macrophage
TCR	T-cell receptor
TET2	Ten-Eleven Translocation Methylcytosine Dioxygenase 2
TGF-β	transforming growth factor beta
TIFAB	TRAF-Interacting Protein with Forkhead-Associated Domain, Family Member B
TIRAP	Toll-interleukin-1 receptor domain-containing adaptor protein
TLR	Toll-like receptor
TME	tumour microenvironment
TNF-α	tumour necrosis factor alpha
TP53	Tumour Protein P53
TRAF	tumor necrosis factor receptor-associated factor
Treg	regulatory T-cell
U2AF1	U2 Small Nuclear RNA Auxiliary Factor 1
VEGF	vascular endothelial growth factor
WT1	Wilms tumour 1
ZRSR2	Zinc Finger CCCH-Type, RNA Binding Motif And Serine/Arginine Rich 2

1 Introduction: Immune Dysregulation in MDS

Myelodysplastic syndromes (MDS) constitute a group of diseases which are distinguished by the presence of one or more unexplained peripheral blood cytopenias, dysplastic hematopoietic differentiation, and variable risk to progress to acute myeloid leukemia (AML). The incidence

of these disorders increases with age, with an average of 70 years (Sekeres 2010). Recurrent mutations and haploinsufficiency of particular genes, related epigenetic changes, altered RNA splicing, and disorder in the bone marrow microenvironment all contribute to the disease phenotype (Cazzola 2020).

Inflammation is involved in many disease processes, such as hypertension, cardiovascular disease, rheumatoid arthritis, rheumatoid heart disease, and systemic lupus erythematosus, which are characterized by impairment of immune cell regulatory mechanisms. Several studies have focused on understanding the immunological abnormalities in in MDS (Banerjee et al. 2019; Xin et al. 2019; Corey et al. 2007; Rosenberg and Sinha 2009; Yang et al. 2015).

The pathogenesis of MDS is heterogeneous and includes abnormalities of both innate and adaptive immune systems, as will be described. Understanding how senescence-dependent changes and mutations impact both hematopoietic stem/progenitor cells (HSPC) and the bone marrow microenvironment is essential to understanding the pathogenesis and progression of the disease (Xin et al. 2019; Wang et al. 2018; Glenthoj et al. 2016; Kornblau et al. 2010; Marvel and Gabrilovich 2015).

The innate immune system was traditionally though to dysregulate HSPC proliferation and trigger apoptotic events contributing to the hallmark ineffective hematopoiesis in MDS. The activation of innate immune cells happens through the interaction between pathogen-associated molecular patterns (PAMPs) or host cell-derived danger-associated molecular patterns (DAMPs) with the Toll-like receptors (TLRs) (Kawai and Akira 2010). The TLR signaling pathway results in activation of mitogen-activated protein kinase cascades and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and leads to transcription of pro-inflammatory cytokines such as interleukin-8, which has been described by de Matos et al. (2017). Intrinsic dysregulation of TLR pathways in MDS HSPC results in hyperactive TLR signalling, including a novel inflammatory form of programmed cell death, known as pyroptosis (Basiorka et al. 2016; Barreyro et al. 2018). Moreover, MDS HSPC have a competitive advantage over normal HSPC in the resultant chronic inflammatory environment, which favours their expansion and disease progression (Muto et al. 2020).

Regarding cytokines, the levels of TNF-α, IFN-γ, TGF-β, IL-6 and IL-8 have been observed to be higher in MDS patients, and associated with both dysregulated inflammatory signaling and myeloid differentiation (Yang et al. 2015; Wang et al. 2018; Kornblau et al. 2010; de Matos et al. 2017). According to Xin et al. (2019), who conducted the first meta-analysis focused on inflammatory cytokine levels in MDS patients, there is a close association between immunological microenvironment disorders and the pathogenesis of MDS, with significantly increased TNF-α, IFN-γ, IL-6 and IL-8 in blood and bone marrow of MDS patients (Xin et al. 2019). In addition to the aforementioned intrinsic dysregulation of inflammatory pathways in HPSC, extrinsic influence of these cytokines from chronic infections or host inflammatory disorders may further foster the MDS clonal advantage and disease progression.

MDS-associated mutations and cytogenetic aberrations may also contribute to the inflammatory milieu. In a study made by Kornblau et al. (2010), some cytokines and chemokines were strongly correlated with certain MDS and AML cytogenetic abnormalities, and influenced MDS outcomes beyond the IPSS-calculated risk (Kornblau et al. 2010). The groups of Karsan and Starczynowski have also demonstrated that haploinsufficiency of micro-RNAs (e.g. miR-145 and miR-146a) and genes in del(5q) MDS (e.g. *TIFAB*) contribute to inappropriate TLR activation, including IL-6 production, by affecting expression of signalling mediators, Toll-interleukin-1 receptor domain-containing adaptor protein (TIRAP) and tumor necrosis factor receptor-associated factor-6 (TRAF6) (Starczynowski et al. 2010; Varney et al. 2015). Moreover, recurrent MDS-associated mutations in epigenetic regulators (e.g. *TET2*, *ASXL1*) and components of the spliceosome machinery (e.g. *SF3B1*, *SRSF2*, *U2AF1*) also appear to converge on innate immune pathways, resulting in excessive

inflammasome activation and inflammatory cytokine production, including IL-6 (Basiorka et al. 2016; Smith et al. 2019; Pollyea et al. 2019).

The expression of at least thirty cytokines, chemokines and growth factors in the peripheral blood and bone marrow have been implicated in MDS pathogenesis and clinical outcomes (Banerjee et al. 2019; Xin et al. 2019; Yang et al. 2015; Wang et al. 2018; Glenthoj et al. 2016; Kornblau et al. 2010; Ganan-Gomez et al. 2015). Increased levels of cell death in bone marrow are a hallmark of lower risk disease. On the contrary, in higher risk MDS, with more aggressive clonal expansion, decreased levels of apoptosis are observed (Yang et al. 2015; Glenthoj et al. 2016; Kerbauy and Joachim 2007). Levels of IFN-γ and IL-6 are associated with apoptosis induction in the bone marrow of MDS patients and higher IFN-γ and IL-6 secretion is generally related to lower-risk MDS. In contrast, immunosuppressive cytokines like IL-10 are more strongly secreted in high-risk MDS (Wang et al. 2018). These studies reflect the importance of inflammatory cytokines in dysregulation of the immunological environment in the pathogenesis of MDS. While they show a range in cytokine profiles between different types of MDS and different studies, they importantly also demonstrate convergence in critical innate immune pathways. Increased intramedullary apoptosis and pyroptosis are important contributors to cytopenias in MDS. Additionally, it is very probable that these immunologic aberrations and pressures play a central role in the course of MDS evolution from low- to high-risk MDS or to AML (Banerjee et al. 2019; Glenthoj et al. 2016; Steensma et al. 2015; Valka et al. 2019; Sallman and List 2019).

The role of adaptive immunity in MDS pathogenesis and progression has been considered, although not as extensively as the molecular connections with innate immunity. CD8+ T-cells may become activated and expanded in response to epitopes on MDS stem cells, resulting in suppression of both malignant and normal hematopoiesis, as reviewed by Wang et al. (2018). This is exemplified in lower-risk MDS with trisomy 8, where the Wilms tumor 1 antigen (WT1) is overexpressed by HPSC, WT1 triggers T-cell suppression of hematopoiesis, and this may be ameliorated by T-cell directed immunosuppressive therapy (Sloand et al. 2011). However, as MDS progresses to high-risk and later stages, there is expansion of regulatory T-cell subsets (Treg) and increased expression of inhibitory checkpoint proteins, which likely facilitate evasion of adaptive immunity by mutant MDS clones (see recent reviews (Wang et al. 2018; Barreyro et al. 2018; Sallman and List 2019; Winter et al. 2020)).

Indeed, it is well described that the tumor microenvironment in MDS and other cancers is immunosuppressive, both inhibiting activated immune cells and activating cells with a suppressive phenotype. Multiple cell types contribute to tumor mediated immune suppression, including Treg, type 2 NKT cells, and tumor associated macrophages (TAMs) (Najjar and Finke 2013). More recently, a group of cells named myeloid-derived suppressor cells (MDSCs) has been considered as responsible for suppressing adaptive immunity and mediating pathological effects seen in MDS (Sica and Massarotti 2017; Chen et al. 2013; Kittang et al. 2015; Eksioglu et al. 2017; Sarhan et al. 2018).

2 MDSC: Pathways of Activation and Pathogenesis in MDS

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immune cells that are defined by their myeloid origin. This group of cells strongly expands in pathological situations such as chronic infections and solid tumors, suppressing immune mediated tumor surveillance and T cell polarization (Marvel and Gabrilovich 2015; Gabrilovich et al. 2007). MDSCs also share other non-immunological functions such as promotion of angiogenesis, tumor local invasion and metastases (Filipazzi et al. 2012; Chesney et al. 2017).

Despite the fact that MDSCs are a phenotypically heterogeneous population of myeloid cells at different stages of maturation, one feature common to all MDSCs is that they show remarkable activity to suppress various non-myeloid immune

cells, such as T-cells, B-cells and natural killer (NK) cells (Filipazzi et al. 2012; Salminen et al. 2019a). MDSCs have also been reported to regulate innate immune responses by modulating the cytokine production of macrophages (Raza and Galili 2012; Lopez-Bujanda and Drake 2017). Three main subdivisions of MDSC have been proposed (Bronte et al. 2016): PMN-MDSCs or G-MDSCs (polymorphonuclear or granulocytic) which account for 70–80% of the MDSC population, M-MDSCs (monocytic) which account for 20–30% of MDSCs, and a smaller fraction of early-stage MDSC (eMDSC) (Lopez-Bujanda and Drake 2017; Bronte et al. 2016). There are some phenotypical differences when human and murine markers are compared. In humans, PMN-MDSCs are identified by the $CD11b^{+}CD14^{-}CD15^{+}$ expression pattern or $CD11b^{+}CD14^{-}CD66b^{+}$, while M-MDSC are characterized by $CD11b^{+}CD14^{+}HLA^{low/-}CD15^{-}$ and eMDSC as lineage (CD3/14/15/19/56)-negative/$HLA\text{-}DR^{-}/CD33^{+}$ (Filipazzi et al. 2012; Bronte et al. 2016; Safarzadeh et al. 2019).

Physiologically, MDSCs are present predominantly in the bone marrow (Nadal et al. 2018). In pathological conditions, such as with cancer, chronic inflammation or autoimmunity, a sustained and aberrant differentiation of myeloid cells occurs, leading to MDSC expansion. Inflammatory factors can modulate myeloid cells in the tumor microenvironment, and having them delivered distantly to hematopoietic organs can change normal myelopoiesis and skew the differentiation of myeloid cells in favor of MDSCs (Umansky et al. 2016). The expansion and activation of MDSC are controlled by a complex network of soluble factors like IL-6, IL-10, IL-1β and IFN-γ, granulocyte-macrophage colony stimulating factor (GM-CSF), M-CSF, G-CSF, vascular endothelial growth factor (VEGF) and TLR ligands (Gabrilovich and Nagaraj 2009; Veglia et al. 2018; Kumar et al. 2016a). Under pathological conditions and mediated by these factors, MDSC can be found in higher proportions in the blood circulation and may be also recruited back to the tumor microenvironment (Kumar et al. 2016b). Moreover, a tumor-microenvironment (TME) that is hypoxic, nutrient-deprived and enriched in pro-inflammatory and suppressive cytokines, chemokines, and oxidative agents such as reactive oxygen species (ROS), nitric oxide (NO) and peroxynitrite, further induces the activation of local MDSCs (Tcyganov et al. 2018; Wang et al. 2013; Consonni et al. 2019; Weber et al. 2018).

MDSC are also defined by their functional ability to suppress immune cell responses (Bronte et al. 2016). This is achieved through the expression of many immune suppressive factors as, for instance, arginase (ARG1), NO and ROS. Unrestrained MDSC activation may, in turn cause DNA mutations and genetic instability.

The specific types of MDSCs use different mechanisms of immunosuppression. The essential difference is that the suppressive PMN-MDSCs produce ROS and ARG1, whereas M-MDSCs predominantly express the inducible nitric oxide synthase (iNOS). However, the common and main mechanism of action associated with the immunosuppressive activities of PMN-MDSCs and M-MDSCs is the metabolic conversion of L-arginine (L-Arg) through either iNOS or ARG1. Because both promote the depletion of the amino acid L-Arg and down-regulation of T cell receptor (TCR) ζ-chain expression, this leads to suppression of the cell cycle and T-cell immunosuppression as a result (Consonni et al. 2019).

MDSC expansion therefore inhibits proliferation and antitumor activity of T cells, decreasing cytokine secretion, recruiting regulatory T cells, and consequently, prohibiting natural killer cell (NK cell) activation, thus hampering the host anti-tumor immune response. Furthermore, MDSC also induce Treg differentiation by secreting IL-10 and TGF-β as well as stimulating tumor angiogenesis by secreting VEGF and basic fibroblast growth factor (Gabrilovich and Nagaraj 2009; Gabrilovich et al. 2012; Schmid and Varner 2012).

Clinical and experimental evidence has shown an association between MDSCs and cancer. A significant increase in MDSCs provokes a propitious immune microenvironment associated with high cancer prevalence, poor prognosis and resistance to therapy (Marvel and Gabrilovich 2015; Kirkwood et al. 2018; Lisha et al. 2018). On the

other hand, the impact of age on MDSCs in humans is not well documented. The mechanisms involved in age-related increase of MDSCs seems to be, at least partly, determined by well-known aging-associated processes, including cellular senescence and chronic low-grade inflammation ("inflammaging"), and likely the skewing of hematopoiesis away from the lymphoid toward the myeloid lineage (Kirkwood et al. 2018; Pawelec et al. 2019; Salminen et al. 2019b). However, the recognition of expanded MDSC in MDS may offer a further genetic connection to aging (Chen et al. 2013).

In 2013, it was reported that MDSC were markedly expanded in the blood (Jiang et al. 2013) and bone marrow (Chen et al. 2013) of MDS patients. The latter study also demonstrated a suppressive effect of MDS MDSC on human erythroid and myeloid progenitor cell growth *in vitro*, implicating MDSC in the ineffective hematopoiesis associated with MDS (Chen et al. 2013). Moreover, with murine models, it was demonstrated that MDSC expansion is driven by pro-inflammatory S100A9, signalling through CD33 and mediated by the induction of immunosuppressive IL-10 and TGF-β (Chen et al. 2013). Independent studies subsequently revealed associations between MDSC and Treg expansion and higher MDS clinical risk (Kittang et al. 2015). Novel therapies are now under consideration, directed towards MDSC and with the goal of ameliorating immunosuppression and improving hematopoiesis (Eksioglu et al. 2017; Sarhan et al. 2018). However, the relationship between these immune cell populations, inflammatory signaling and recurring mutations in MDS is not completely understood. The influence of different factors in expansion and activation of MDSCs such as PGE2, VEGF, IL-6, IL-10 and S100A8-A9 has been shown (Rosenberg and Sinha 2009; Marvel and Gabrilovich 2015; Najjar and Finke 2013; Gabrilovich and Nagaraj 2009; Pawelec et al. 2019). Due to the profile of inflammatory cytokine changes with the course of disease, current studies have focused on understanding the abnormalities in immunologic profile in different myeloid disorders, mainly in MDS and AML, and other proposals to deplete the key innate immune cellular effectors, MDSC, are still currently in development (Sallman and List 2019; Pawelec et al. 2019).

3 Considerations for Clonal, Pre-MDS States: CHIP and CCUS

Major breakthroughs in the molecular and genetic basis of MDS have recently been achieved. Genetic lesions, namely recurrent somatic point mutations and/or small insertions/deletions in >40 different genes, have now been associated with MDS pathogenesis (Cazzola 2020; Cull and Rauh 2017; Claus and Lubbert 2003; Issa 2010; Sperling et al. 2017). These mainly occur in genes regulating RNA splicing (e.g., *SF3B1, SRSF2, U2AF1, ZRSR2*), DNA methylation (e.g., *TET2, DNMT3A, IDH1/IDH2*) and chromatin accessibility (e.g., *ASXL1, EZH2, STAG2, RAD21*), transcription factors (e.g. *RUNX1, GATA2, ETV6*), signal transduction (e.g. *CBL, JAK2, NRAS*) and the response to DNA damage (e.g. *TP53, PPM1D*). In the case of *SF3B1*, the presence of mutations is incorporated into the current iteration of the World Health Organization classification of MDS, with a recent proposal to recognized *SF3B1*-mutant MDS as an even more distinct diagnostic entity (Malcovati et al. 2020).

Presently, other MDS-associated mutations are not considered diagnostic of MDS on their own. This is because at least 10–15% of healthy older persons with no hematologic disease acquire somatic mutations that overlap with MDS, drive clonal expansion and, eventually, what is now called clonal hematopoiesis of indeterminate potential (CHIP) (Steensma et al. 2015). Although most individuals who acquire CHIP during aging will never develop MDS, the presence of an MDS-associated somatic mutation, such as in *DNMT3A*, *ASXL1* or *TP53* is a strong predictor of the development of subsequent hematologic malignancy and is associated with worse overall survival (Park et al. 2019; Yoshizato et al. 2015). The presence of a recurrent mutation and otherwise

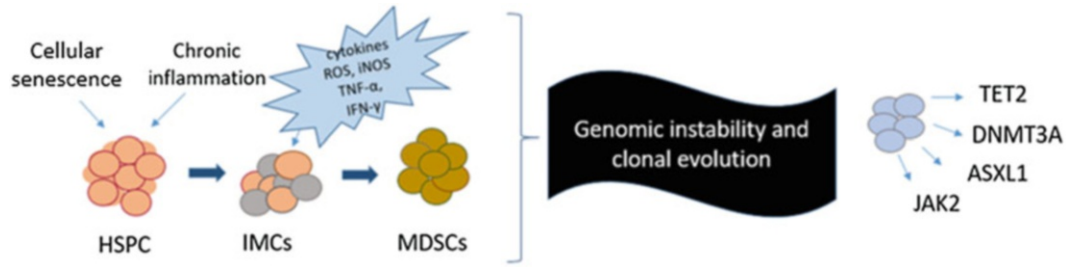

Fig. 1 Some of the main pathways involved in MDS pathogenesis and progression. An aging and inflammatory bone marrow microenvironment induced by cellular senescence and chronic immune stimulation leads to MDSC accumulation and activation. Inflammatory cytokines and soluble factors, such as ROS and iNOS, contribute to increased apoptosis and pyroptosis of HSPCs as well as genomic instability. Somatic mutations contribute to further dysregulation of immune system, suppression of normal hematopoiesis, clonal evolution and susceptibility to leukemic transformation. *HSPC* Hematopoietic stem and progenitor cells, *IMCs* Immature myeloid cells; *MDSCs* Myeloid-derived suppressor cells, *ROS* Reactive oxygen species, *iNOS* Inducible nitric oxide synthase, *TNF-a* Tumor necrosis factor-alpha, *IFN-γ* Interferon gamma, *TET2* Tet methylcytosine dioxygenase 2, *DNMT3A* DNA methyltransferase 3A, *ASXL1* Additional sex combs like 1, *JAK2* Janus Kinase 2

unexplained cytopenias (clonal cytopenias of undetermined significance, CCUS) can be suggestive of progression to MDS, although in this case more specific morphologic criteria are mandatory (Sperling et al. 2017; Cargo et al. 2015; Kwok et al. 2015). A subsequent study with longitudinal follow-up suggests it may be possible to predict patients with CCUS at greatest risk of progression to MDS or other myeloid neoplasm and that, effectively, CCUS patients with particular mutational features may have presumptive evidence of early MDS (Malcovati et al. 2017).

As described, there is a complex process involved in the pathogenesis of MDS, especially mechanisms directly correlated with myeloid-mediated inflammation, the accumulation of genetic damage, immunosuppression and related selective pressures during the evolution of malignant clones (Steensma et al. 2015; Hosono 2019) (Fig. 1). Although we have mainly focused on these aspects in the context of MDS, these processes are likely at play as early as the CHIP phase and into CCUS. For example, common drivers of CHIP and MDS, mutations in *TET2* and *DNMT3A*, have been associated with inflammation and immune cell alterations in humans and murine models, as recently reviewed (King et al. 2020; SanMiguel et al. 2020; Ferrone et al. 2020; Cook et al. 2020). Moreover, spliceosomal mutations (e.g. *SF3B1*, *SRSF2*, *U2AF1*) also appear to converge on innate immune pathways, resulting in excessive inflammasome activation and inflammatory cytokine production, including IL-6 (Smith et al. 2019; Pollyea et al. 2019). Finally, our group has demonstrated increased ARG1 expression in *Tet2*-mutant macrophages (Cull et al. 2017) and in MDS patients with *DNMT3A* and *TET2* mutations (Cull et al. 2018). This could signify a myeloid suppressive phenotype (reminiscent of MDSCs) in response to chronic inflammation but more studies are required to map the relationship between immune dysregulation and mutations in the progression from CHIP to CCUS and MDS. The comprehension of genetic lesions, genomic instability and dysregulated immune response are important to better understand MDS pathogenesis, progression and predictive factors of response to therapy.

4 Conclusions

Though the pathogenesis in MDS is now much more understood, the factors involved in this heterogeneous process are still an attractive and constant focus of research. Clinical and experimental evidence suggest an important link between genetic, epigenetic, and immune systems in the

pathogenesis and progression of MDS. Ongoing studies are looking at more specific molecular and immune pathways and targets with potential clinical significance, notably the role of the inflammatory marrow environment and MDSCs in MDS. Translation from understanding the complex molecular and immunological pathophysiology of MDS to the identification of new targets and novel treatment options are long awaited.

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Adv Exp Med Biol - Cell Biology and Translational Medicine (2021) 12: 11–37
https://doi.org/10.1007/5584_2020_577

Published online: 11 September 2020

Stem Cell Aging and Regenerative Medicine

Debojyoti De, Parimal Karmakar, and Debalina Bhattacharya

Abstract

Stem cells are a promising source for regenerative medicine to cure a plethora of diseases that are currently treated based on either palliative or symptomatic relief or by preventing their onset and progression. Aging-associated degenerative changes in stem cells, stem cell niches, and signaling pathways bring a step by step decline in the regenerative and functional potential of tissues. Clinical studies and experiments on model organisms have pointed out checkpoints that aging will inevitably impose on stem cell aiming for transplantation and hence questions are raised about the age of the donor. In the following discourse, we review the fundamental molecular pathways that are implicated in stem cell aging and the current progress in tissue engineering and transplantation of each type of stem cells in regenerative medicine. We further focus on the consequences of stem cell aging on their clinical uses and the development of novel strategies to bypass those pitfalls and improve tissue replenishment.

D. De and P. Karmakar
Department of Life science and Biotechnology, Jadavpur University, Kolkata, India

D. Bhattacharya (✉)
Department of Microbiology, Maulana Azad College, Kolkata, India
e-mail: debalina.bhattacharya13@gmail.com; debalina.bhattacharya@maulanaazadcollegekolkata.ac.in

Keywords

Aging · Regeneration · Regenerative medicine · Senescence · Stem cells

Abbreviations

ADSC	Adipose tissue-derived stem cell
ASC	Adult stem cell
BMSC/BMDSC	Bone marrow-derived mesenchymal stem/stromal cell
CSC	Cardiac stem cell
DNMT	DNA methyltransferase
EPC	Endothelial progenitor cell
ESC	Embryonic stem cell
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GSC	Germline stem cell
GVHD	Graft versus host disease
HAT	Histone acetyltransferase
HDAC	Histone deacetylase
HIF	Hypoxia-Inducible Factor
HSC	Haematopoietic stem cell
ICM	Inner cell mass
iPSC	Induced pluripotent stem cell
ISC	Intestinal stem cell
LDHA	Lactate dehydrogenase A
MDSC	Muscle-derived stem cell
MSC	Mesenchymal stem cell
NAC	N-acetylcysteine