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Review Article

Bone Marrow Microenvironment Involvement in t-MN: Focus on Mesenchymal Stem Cells

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Abstract. Therapy-related myeloid neoplasms (t-MN) are a late complication of cytotoxic therapy (CT) used in the treatment of both malignant and non-malignant diseases. Historically, t-MN has been considered to be a direct consequence of DNA damage induced in normal hematopoietic stem or progenitor cells (HSPC) by CT. However, we now know that treatment-induced mutations in HSC are not the only players involved in t-MN development, but additional factors may contribute to the onset of t-MN.

One of the known drivers involved in this field is the bone marrow microenvironment (BMM) and, in particular, bone marrow mesenchymal stem cells (BM-MSC), whose role in t-MN pathogenesis is the topic of this mini-review.

BM-MSCs, physiologically, support HSC maintenance, self-renewal, and differentiation through hematopoietic–stromal interactions and the production of cytokines. In addition, BM-MSCs maintain the stability of the BM immune microenvironment and reduce the damage caused to HSC by stress stimuli.

In the t-MN context, chemo/radiotherapy may induce damage to the BM-MSC and likewise alter BM-MSC functions by promoting pro-inflammatory response, clonal selection and/or the production of factors that may favor malignant hematopoiesis.

Over the last decade, it has been shown that BM-MSC isolated from patients with *de novo* and therapy-related MN exhibit decreased proliferative and clonogenic capacity, altered morphology, increased senescence, defective osteogenic differentiation potential, impaired immune-regulatory properties, and reduced ability to support HSC growth and differentiation, as compared to normal BM-MSC.

Although the understanding of the genetic and gene expression profile associated with ex vivo-expanded t-MN-MSCs remains limited and debatable, its potential role in prognostic and therapeutic terms is acting as a flywheel of attraction for many researchers.

Keywords: t-MN, Bone marrow Microenvironment, Mesenchymal stem cells.

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Introduction. Therapy-related myeloid neoplasms (t-MN), or MN post cytotoxic therapy (MN-pCT) include, according to the 2022 WHO classification[1] and its previous editions,[2-3] therapy-related acute myeloid

leukemia (AML), myelodysplastic syndromes (MDS), and myelodysplastic/myeloproliferative neoplasms (MDS/MPN).

t-MNs are a late complication of cytotoxic agents (chemo and/or radiation therapy) used in the treatment of both malignant (solid or hematological) and non-malignant (mostly autoimmune) diseases.

They are an emerging problem of our aging society, where the newer therapeutic drugs and ameliorated cancer management protocols have improved the life expectancy of cancer patients in the last decades.[4] This results in an increase in patient number at risk of developing this late treatment-related complication,[5] characterized by poor prognosis (5-year overall survival <10%)[6] and refractoriness to current standard treatment strategies, still remaining an unmet clinical need of cancer survivorship programs.[7]

t-MN accounts for approximately 10–20% of newly diagnosed cases of AML or MDS and can occur at any age.

Historically, t-MN has been considered to be a direct consequence of DNA damage induced in normal hematopoietic stem or progenitor cells (HSPC) by CT. However, in recent years advances in deep sequencing techniques have faltered this historical theory and have given way to a multi-hit model of t-MN where both intrinsic and extrinsic factors contribute to its development.[8]

According to this multi-step pathogenesis, patient-related factors, including age, type, and treatment of primary disease, in the presence of germ-line variants, together with acquired factors, such as clonal hematopoiesis of indeterminate potential (CHIP) and inflammation, may all contribute to lay the groundwork for the development of myeloid diseases.[7,9-15] The subsequent CT may later favor additional hit development, such as the acquisition of genetic and/or cytogenetic abnormalities, the selection of abnormal hematopoietic clones (e.g. with TP53 mutations and/or unfavorable karyotype) and changes in the bone marrow microenvironment (BMM), resulting in t-MN onset.[8,16-19]

In this mini-review we synthesize recent findings about the involvement of BMM in MN *de novo* (MDS and AML) and therapy-related pathogenesis with a deeper focus on the role of bone marrow mesenchymal stem cells (BM-MSC). For all other players involved in the pathogenesis of t-MN (inherited predisposition, exposure to genotoxic agents, clonal selection and abnormal bone marrow microenvironment), we refer you to two recent reviews.[8,16]

Mesenchymal Stem Cell: an Intriguing Cell Within the Bone Marrow Cellular Metropolis. Human BM can be considered a cellular metropolis, composed of highly vascularized multicellular tissue containing self-renewing HSCs, which generate progeny that progressively differentiates into mature myeloid, erythroid, and lymphoid cells. These HSCs in the BM are surrounded by a plethora of cellular (endothelial cells, osteo-lineage cells, adipocytes, MSC, fibroblasts, macrophages, neutrophils, megakaryocytes, and immune cells) and noncellular (extracellular matrix and soluble factors) components. BMM cells form distinctively organized niches (endosteal, perivascular, arteriolar, and central medullary), with each of these anatomical regions in the bone having a specialized role in maintaining the quiescence, homing and mobilization of the HSC.[20-24] Collectively, these different cell types interact with each other and HSC both through direct contact-based regulation and the secretion of key signaling molecules and, in this way, participate in the maintenance of hematopoietic homeostasis.[25]

In this mini-review, we focus on mesenchymal stem cells, one of the players involved in bone marrow homeostasis. Mesenchymal stem cells or mesenchymal stromal cells are multipotent stem cells of mesodermal origin (**Figure 1**) that can be isolated from adult and fetal tissues. In the bone marrow, they represent a rare population, accounting for $1/10^4$ mononuclear cells. BM-MSCs have a fibroblast-like morphology. According to the International Society for Cellular Therapy,[26] a cell to be defined as a BM-MSC must comply with 3 minimum criteria:

- ability to adhere to a plastic substrate under standard culture conditions (unlike HSC grow in suspension)
- immunophenotype positive for main mesenchymal markers such as CD73, CD90, CD105 and negative for main hematopoietic markers such as CD14, CD79, CD34, CD45, HLA-DR
- trilinear differentiative potential (osteogenic, adipogenicity and chondrogenic lineages).

MSCs are distinct from BM stromal cells, which are mostly comprised of hematopoietic supporting fibroblasts, differentiated from MSC. In BM, MSCs can be located at different anatomical sites (central sinus, trabeculae, endosteal region, and compact bone). These locations are also sites of hematopoietic activity in which the function of HSC is supported by BM-MSC and their differentiated cells (e.g. fibroblasts, adipocytes and osteoblasts). Thus, the functional relationship between MSC and hematopoietic activity are part of the process of maintaining BM homeostasis.

Physiologically, BM-MSCs have dual functions (**Figure 2**): support hematopoiesis and regulate, by inhibiting, the immune response. BM-MSCs regulate the balance between self-renewal and differentiation of HSC through the production of various soluble factors (such as growth factors and cytokines) as well as surface molecules.

Moreover, BM-MSCs have immunoregulatory properties by maintaining the stability of the BM

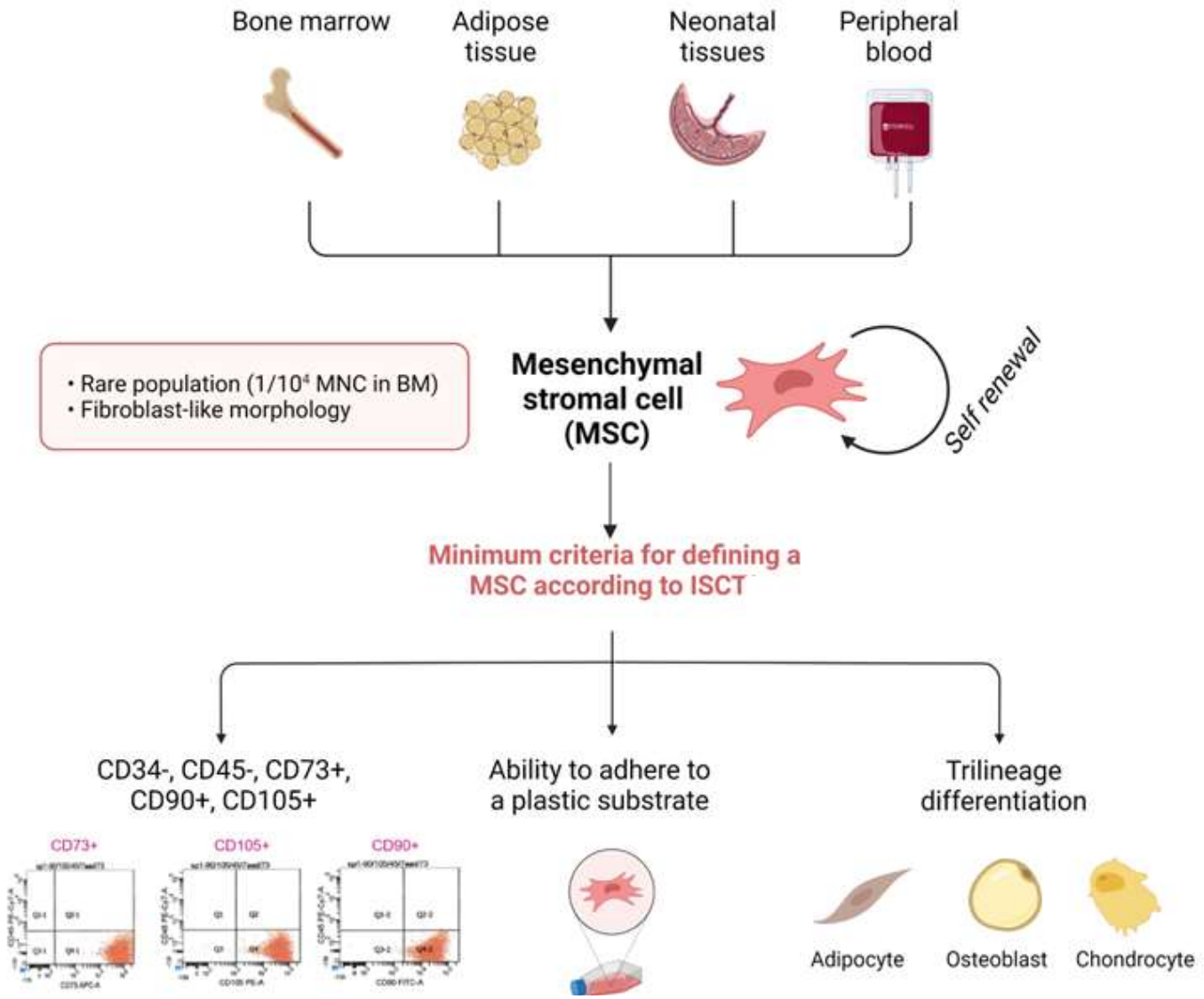

Figure 1. Main features of mesenchymal stem cells. Created with BioRender.com. **Legend:** MNC: MonoNuclear cell; BM: Bone Marrow; ISCT: International Society of Cellular Therapy.[26]

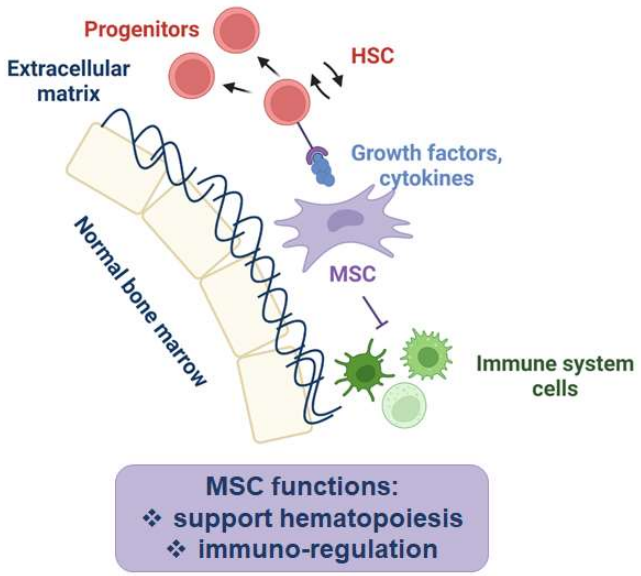

Figure 2. Simplified picture of the function of mesenchymal stem cells in a healthy bone marrow. Created with BioRender.com.

immune microenvironment and reducing the damage caused to HSC by stress stimuli.

Involvement of BM-MSC in *de novo* MN Development. Recent studies have highlighted the role of a complex bidirectional crosstalk between HSC and the BMM in normal hematopoiesis, as well as in the pathogenesis of myeloid diseases.[27] Emerging data suggest that alterations of BM-MSC, an important component of the BMM,[28] may play a role in the pathogenesis of myeloid neoplasms, both *de novo* and therapy-related,[29-36] although the mechanisms are not yet fully understood.

The first experimental evidence supporting the crucial role of BMM and MSC in the initiation and progression of myeloid malignancies derived from *in vivo* models. Using murine genetic models, several groups have shown that specific genetic changes in the microenvironment, including reduced function of genes such as RAR-γ, Rb, Mib1, IκBα, Sipa1, Dicer1 and

concordant loss of the EGR1, APC, and TP53 in non-hematopoietic cells, may have a pathophysiological significance in the genesis of hematological malignancies, in particular for the creation of a premetastatic niche that supports the growth and spread of clonal neoplastic cells.[37-41]

In a mouse model of pre-leukemia, Zambetti and colleagues[42] established a concept of mesenchymal niche-induced genotoxic stress in HSC, providing conceptual and mechanistic insights into the link between inflammation and cancer. The authors showed that perturbation of mesenchymal cells in a mouse model of the pre-leukemic disorder Shwachman-Diamond syndrome induces mitochondrial dysfunction, oxidative stress, and activation of DNA damage responses (DDR) in HSPC through p53-S100A8/9-TLR4 inflammatory signaling as a common driving mechanism of genotoxic stress.[42]

Taken together, all these mouse model studies strongly support the hypothesis that an altered BMM provides "fertile ground" for the expansion of neoplastic cells *in vivo*.

Moreover, BM-MSCs influence leukemic cells and are essential for the propagation of human MDS-HSC *in vivo* in xenograft models. Medyouf and colleagues showed the inability of human MDS stem cells to propagate in a cell-autonomous manner and demonstrated that co-injection of MDS-HSC with MDS-MSC in NSG mice results in a significantly higher percentage of engraftment compared single injection of MDS-HSC in the bone marrow of xenografted mice analyzed 16–28 weeks post-transplant.[33] Therefore, this patient-derived xenograft model provides functional and molecular evidence that MN is a complex disease that involves both the hematopoietic and stromal compartments. An independent study has also demonstrated that multiplex gene editing to confer leukemic drivers in healthy human HSPC is insufficient for the development of leukemia after transplantation in mice, supporting the need for a dysplastic stroma in disease initiation.[43]

In summary, BM-MSC may influence hematopoietic cells and similarly, hematopoietic cells can induce remodeling of BM-MSC. After long periods of exposition to neoplastic hematopoietic cells, healthy BM-MSCs can be reprogrammed, acquiring functional alterations, to work in cooperation with leukemic cells and propagate the disease.

Compared to BM-MSC isolated from healthy donors (HD), BM-MSC isolated from patients with *de novo* MDS/AML are structurally, epigenetically and functionally altered (**Figure 3**).[29-36] Unlike the BM-MSC isolated from HD having the characteristic fibroblast-like appearance, patient-derived BM-MSC present an altered morphology, are larger and appear flattened and disorganized. Moreover, they exhibit decreased

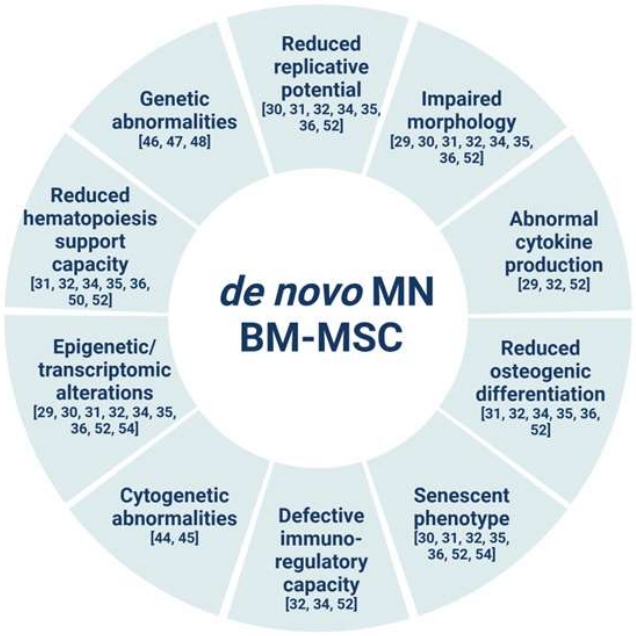

Figure 3. Main alterations observed in ex vivo-expanded *de novo* MN BM-MSC. Created with BioRender.com.

proliferative and clonogenic capacity, reduced osteogenic differentiation, increased senescence and impaired immunoregulatory properties.[29-36]

The clonal origins of MN-MSC have always been questioned. There are contradictory reports about the presence of 'MN related-gene' mutations or chromosomal abnormalities in MN MSC.[44-51] Regarding chromosomal analysis, Blau and colleagues reported BM-MSC karyotype abnormalities in a fraction of MDS/AML patients (15-30%), but not in healthy controls. Of note, these studies reported the occurrence of non-clonal chromosomal aberrations in BM-MSC isolated from patients with MDS and AML, which only very rarely correspond to the cytogenetic markers observed in the hematopoietic leukemic clone of the same individual.[44-45] In the same line, our group investigated the frequency of recurrent mutations of epigenetic and spliceosome genes in paired bone marrow hematopoietic and mesenchymal cells isolated from patients with different myeloid malignancies. We found no mutations for any of the studied genes in the MSC compartment, both in carriers of mutations in the hematopoietic compartment and in wild-type patients.[46]

Furthermore, MN–MSCs have an altered expression of key molecules involved in the interaction with HSPC, in particular Osteopontin, Jagged1, Kit-ligand and Angiopoietin as well as several chemokines.[32,52] Functionally, this translated into a significantly reduced ability of MN-MSCs to support normal HSC in long-term culture-initiating cell assays. When MDS HSC are cultured with MSC from healthy donors, their clonogenic capacity is partially restored.[32] These data indicate that diseased bone marrow cells are likely to

play an active role in the ‘‘reprogramming’’ of their BM niche during disease development and/or progression by possibly converting it into a self-supportive one.

A similar reduction in hematopoiesis support can be reproduced by silencing the transcription factor FOXM1 in BM-MSC. The repression of FOXM1, the transcription factor that drives G2/M transition, in elderly mitotic cells, increased chromosome mis-segregation and correlates with an early senescence-associated phenotype.[53] Recently, our group have showed that the silencing of FOXM1 mRNA in HD-MSCs recapitulates the downregulation of FOXM1 and its mitotic targets observed in MSC *de novo* and therapy-related MDS.[54] Furthermore, FOXM1 silencing is able to reduce the supportive capacity of hemopoiesis as demonstrated by the reduction of granulocyte colonies numbers after coculture of healthy HSC with MSCs in which FOXM1 was silenced.[54]

Involvement of BM-MSC in Therapy-related MN Development. For just over a decade, we have known that t-MN development is a multifactorial process resulting from complex interactions between an underlying germline genetic susceptibility, the stepwise acquisition of somatic mutations in HSC, the clonal selection pressure exerted by CT and alterations in the BMM.[8] However, although in the literature many works comparing the mutational/transcriptomic/epigenetic/cytogenetic profiling of *de novo* and therapy-related MN at the level of the hematopoietic compartment (HSC or HSPC) are present,[55-59] extensive studies concerning the involvement of BM-MSC in the pathogenesis of t-MN are only recently emerging.[30,46,60] One of the first works in this regard was conducted by our group in 2016 on a cohort of patients with multiple hematologic malignancies, including *de novo* MDS/AML and therapy-related myeloid neoplasms of whom we isolated and ex vivo-expanded BM-MSC.[30] In t-MN BM-MSCs, we observed an altered morphology and a decreased proliferative and clonogenic potential compared to HD-MSC.[30] Moreover, no mutations in genes involved in splicing, DNA methylation, and the TP53 gene have been identified in t-MN MSC.[46,60]

More recently, to better decipher the microenvironmental changes induced by CT *vs.* neoplasia, Kutyna and colleagues performed a multi-omic (transcriptome, DNA damage response, cytokine secretome, and functional profiling) characterization of BM-MSC both from patients with t-MN, MN, and another cancer but without cytotoxic exposure, typical primary MN, and age-matched controls.[60] The authors showed that t-MN MSCs are distinct from HD-MSCs but are also distinct from other primary MNs, developing apart from cytotoxic exposure. Strikingly, among all studied populations, t-MN appeared to have the greatest defect in terms of morphology, proliferative capacity, and support to hematopoiesis.

What is the role of cytotoxic therapy in this context? The role of CT is complex and not yet clear. Cytotoxic therapy has been shown to exert several effects on the BMM, including a pro-inflammatory response with the consequent release of inflammatory cytokines (e.g., TNFα, TGFβ, and IL-6) and release of reactive oxygen species (ROS) by MSC with resultant genotoxic damage to HSC.[8,41]

Stoddart and colleagues described cooperative effects of exposing both the BMM of recipient mice and donor HSPC to the alkylating agent N-ethyl-N-nitrosourea (ENU) in a genetically model of therapy-induced MDS and AML characterized by chromosome 5q deletions.[41] In detail, the haploinsufficiency of two del(5q) genes (EGR1 and APC), together with TP53 knockdown, in a mouse model, produces a high frequency of myeloid diseases following concurrent treatment of both hematopoietic cells and the BM stroma with ENU, but not after treatment of either alone.[41] In addition, loss of TP53 with EGR1 and APC was required to drive the development of a transplantable leukemia and accompanied by the acquisition of somatic mutations in DDR genes. ENU treatment of MSC induced cellular senescence and led to the acquisition of a senescence-associated secretory phenotype (SASP), which is a critical microenvironmental alteration in the pathogenesis of t-MN.[41,56]

Similarly, t-MN *ex vivo* expanded BM-MSC showed a profoundly senescent phenotype with a characteristic flattened morphology, defective regenerative capacity, high p21 and β-Galactosidase expression, and a SASP with secretion of pro-inflammatory cytokines, chemokines, and proteases.[60] Interestingly, the level of senescence in t-MN BM-MSCs was independent of the latency period, the interval between completion of CT and t-MN diagnosis. High levels of senescence were evident both in t-MN BM-MSC with short (3–4 months) and long latency (up to two decades following CT).[60] Moreover, BM-MSCs derived from t-MN had higher baseline DNA damage and higher intracellular ROS levels compared to HD BM-MSC and were highly sensitive to CT (e.g., Doxorubicin).[60]

Recently, Özdemir and colleagues showed that alterations in the BM niche may play a critical/driver role in the development of secondary AML. The treatment with the chemotherapeutic agent Etoposide of HD BM-MSC is able to induce an increased expression of selected genes involved in xenobiotic metabolism, DNA double-strand break response, heat shock response, and cell cycle regulation such as CYP1A1, GAD34, ATF4, NUPR1, CXCL12, KLF4, CCNB1.[61]

Similarly, the high senescence level observed in t-MN BM-MSCs is due to a defect in the DDR pathway, resulting in permanent DNA damage after exposure to

cytotoxic therapy.[60,62] Sequential patient sampling showed that exposure to DNA-damaging agents leads to pro-inflammatory stromal defects and irreversible damage evident many years before the onset and diagnosis of t-MN. These data underscore the role of senescence in the pathogenesis of t-MN and provide a valuable resource for future therapeutics with repercussions for patients treated with chemotherapy or radiotherapy.

Despite their dormant state, t-MN stromal cells were metabolically highly active with a switch toward glycolysis and secreted multiple pro-inflammatory cytokines (IFNγ, IL-7, IL-1β, IL-13, IL-15, and EGF) indicative of a senescent-secretory phenotype that inhibited adipogenesis.[60] t-MN MSC exhibited a selective defect in adipocyte differentiation that was experimentally mimed by treating healthy BM-MSC with senescence-secreted cytokines IL-1β and IFNγ. Treatment of HD BM-MSC with IL-1β, IFNγ, IFNα, or a cocktail of cytokines (IL-1β, IL-13, IL-15, IL-6, IFNα, and IFNγ) profoundly inhibited adipogenesis *in vitro*, demonstrating a potential causative role of senescence-secreted cytokines in inhibiting adipogenesis. These data suggest that the secretome is modifying stromal fate.[60]

Finally, Kutyna and colleagues showed that senolytic agents Dasatinib and Quercetin alone or in combination effectively reduced the senescence burden and restored the differentiation potential of t-MN BM-MSC, indicating a possible role of senolytic therapies in modulating t-MN long-term. Senolytics, including Dasatinib and Quercetin, have been shown to selectively eliminate senescent cells from both humans and mouse,[63-67] with evidence that sufficient restoration of function may occur without eliminating all senescent cells.[63,65,68] Indeed, in the study of Kutyna and colleagues, senolytics restored the defect in adipogenesis differentiation in t-MN.

Currently, there is an enhanced focus on extrinsic, age-related changes in the BM microenvironment that accompany the development of t-MN. One of the most prominent changes associated with aging is the accumulation of senescent BM-MSC within tissues and organs. In comparison with proliferating cells, senescent cells display an altered secretome comprising proteases, inflammatory cytokines, and growth factors that may render the local microenvironment favorable for cancer growth.[69] There is emerging evidence that BM-MSC senescence may contribute to age-related hematopoietic decline and cancer development. Moreover, CT creates an environment that selects for pre-existing mutant clones at the expense of normal HSCs. In this context, DNA damage-induced competition led to a selective clonal advantage of HSCs and hematopoietic progenitor cells with reduced p53 function in mouse BM chimeras, reminiscent of the CHIP phenotype, via growth arrest and senescence-related gene expression in cells with higher p53 activity.[70]

Summary and Future Prospective. Therapy-related myeloid neoplasms are a multifactorial disease resulting from complex interactions between a germline genetic susceptibility, the acquisition of somatic mutations in hematopoietic stem cells, the clonal pressure exerted by cytotoxic therapies, and alterations of the bone marrow microenvironment.

BM-MSC isolated from patients with t-MN present several alterations (e.g., pro-inflammatory and senescent phenotype), both intrinsic and extrinsic, contributing to the pathogenesis of t-MN and could provide a valuable resource for future therapeutics. It would be interesting to understand whether the highly pro-inflammatory SASP observed in BM-MSC-derived from t-MN could initiate or promote a form of clonal hematopoiesis, eventually progressing to t-MN and whether it could become an effective therapeutic target.

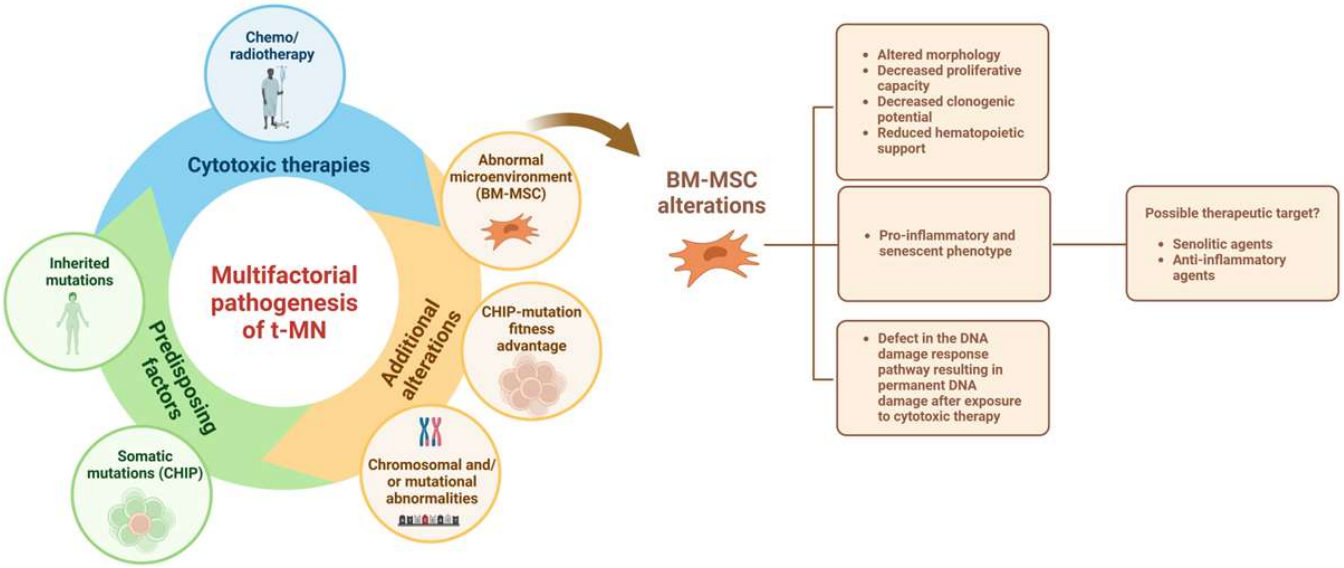

Figure 4. Contribution of BM-MSC in t-MN development. Created with BioRender.com.

In summary, these recent studies shed new light on the complex pathogenesis of t-MN and establish a model for future biological and preclinical investigation.

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