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Review Article

Exploring the molecular mechanisms between lymphoma and myelofibrosis

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Abstract: Lymphoma is a heterogeneous malignant tumor with an increasing annual incidence. As the lymphoma progresses, bone marrow (BM) invasion gradually appears. Myelofibrosis (MF) can accompany a variety of hematological malignancies, including lymphoma, and multiple myeloma. The prognosis of lymphoma patients with myelofibrosis is poor, and a fundamental reason is that there are few studies on the correlation and pathogenesis of the two diseases. In this review, we examine the potential pathogenesis and the correlation of the two diseases.

Keywords: Lymphoma, myelofibrosis, JAK-STAT signaling pathway, tumor microenvironment

Introduction

Lymphoma is a large group of hematological malignancies, which originate from the lymph nodes and/or extra-nodal lymphoid tissues, and is categorized into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). In recent years, lymphoma has been associated with high mortality and morbidity rates in China [1]. The World Health Organization (WHO) GLOBOCAN 2020 reported that in 2020, there were 544,352 new cases and 259,793 deaths from NHL, ranking 13th among all new cases and 12th among all deaths of malignant tumors [1, 2]. NHL progression is associated with an increased risk of bone marrow (BM) invasion and a high incidence of myelofibrosis (MF). MF is categorized into two clinical subtypes: primary myelofibrosis (PMF) and secondary myelofibrosis (SMF). PMF is characterized morphologically primarily by proliferation of abnormal megakaryocytes in the BM, which is associated with increased polyclonally of fibroblasts that drive secondary increases in reticulin and/or collagen, and shows fibrosis, angiogenesis and osteosclerosis. The excessive activation of the Janus kinase/signal transducers and activators of transcription (JAK-STAT) signaling pathway and increased megakaryocyte proliferation are fundamental to PMF pathology. Moreover, mutations targeting JAK, MPL and CALR directly trigger JAK-STAT pathogenesis [3]. Following the 2016 revision of WHO classification, PMF can be divided into early/pre-fibrotic stage of PMF (pre-PMF) and overt PMF [4]. In contrast to PMF, SMF is diagnosed on the basis of defined underlying disease presence, including but not limited to connective tissue disease, lymphoma, leukemia, multiple myeloma, BM metastasis from solid tumors, chronic inflammation, infection, chemoradiotherapy drugs, hyperparathyroidism, and rickets [5]. However, cases of malignant lymphoma combined with MF are rare and the exact pathogenesis of this disease remains unknown. In this review, we examine the potential pathogenesis and the correlation of the two diseases.

Potential association

The association of lymphoma and MF in the same patient is a relatively uncommon event, described mostly sporadically in case reports. Biologically, it has been speculated that the co-occurrence of myeloproliferative neoplasms (MPNs) lymphoma may be sustained by abnormal cloning and genetic changes of early hematopoietic progenitor cells [6, 7]. A report by Rumi et al. described that the increased risk of lymphoproliferative neoplasms (LPN) in MPN

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patients may be multi-factorial, including genetic susceptibility (i.e., p53, VHL, SNPs), acquired mutations (JAK2V617F), and impaired immune monitoring [8, 9]. Laurenti et al. described Lymphoma patients with or without MPN show indicating differences at the molecular level, such as citrate synthase, DNAJA2 protein and IDH2 protein [10]. A retrospective study showed a 6.6% incidence of combined SMF in lymphoma cases [11]. It has been suggested that MF is the result of lymphoma invading the BM [12], while others believe that MF can precede or be in co-existence with lymphoma [13-15]. In a large retrospective analysis by Porpaczy et al. JAK/STAT1 pathway inhibition and the preexisting B-cell clone are associated with an elevated frequency of aggressive B-cell lymphomas (16-fold increased risk) [16]. Another study reported by Rumi et al. in the absence of a B-cell clone, did not find increased risk of lymphoma in MPN patients treated with JAK inhibitor [17]. A patient was treated with JAK inhibitor and didn't develop aggressive lymphoma 24 months after stopping [18]. This suggests that the preexisting B-cell clone may further contribute to lymphoma development. Similarly, a review on the occurrence of lymphoma in patients with MPN supports this conclusion [19].

Moreover, sporadically literature of MF after lymphoma have been published, mostly based on case reports. It may be related to abnormal activation of the JAK/STAT signaling pathway and the release of cytokines produced by lymphoma cells such as transforming growth factor-β (TGF-β), plated-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (b-FGF), tumor necrosis factor α (TNF-α), and interleukin (IL)-1β, and IL-6 [15]. These cytokines play an important role in the development of stromal proliferation, and disrupt interactions amongst the megakaryocytes, osteoblasts, stromal cells and myofibroblasts. The ensuing affected angiogenesis, stability of extracellular matrix and mesenchymal stromal cells leading to fibrosis. Importantly, the microenvironment, mutations in functional oncogenes and epigenetic genes such as TET2, IDH2, EZH2, ASXL1 as well the presence of specific inflammatory cytokines may be linked to fibrotic aspects of the pathology [20, 21].

Potential pathogenesis

Patients are diagnosed with lymphoma and MF more frequently in the population than expected, which has led to the hypothesis that, in some cases, they may be pathogenetically related. The pathogenesis of SMF in patients with primary lymphoma may be related to the activation of signaling pathways and cytokine secretion. Furthermore, disease development is not the result of a single mechanism; driver mutations, the tumor microenvironment, and other signaling pathways such as nuclear factor-κB (NF-κB), also play the same role. Their interactions together promote lymphoma with myelofibrosis.

JAK-STAT signaling

Although lymphoma is a known cause of MF, the pathophysiology of MF in lymphoma patients remains unknown. It is speculated that the pathogenesis of SMF may be related to the abnormal activation of JAK-STAT signaling and the cytokines produced by lymphoma cells, such as TGF-β, PDGF, TNF-α, IL-1β, and b-FGF. Hu's review has elucidated that VEGF, PDGF, TGF-β and other anti-inflammatory cytokines (IL-4, IL-6, IL-10, IL-13) phosphorylate different JAK sites and activate different STATA pathways [22]. The signaling cascade of the JAK/STAT signaling pathway includes JAK activation, tyrosine phosphorylation, and STAT recruiting. The constitutive activation of the JAK-STAT signaling pathway is triggered by mutations in JAK2, CALR or MPL oncogene. However, JAK2 mutations do not always differentiate between lymphoma patients with or without concurrent MF, as approximately 10%-15% of MF patients do not have mutations targeting this factor [23]. Additionally, "subclone" mutations in certain genes, including TET2, DNMT3A, ASXL1, EZH2, U2AF1, SF3B1, SRSF2, TP53, and other signaling (CXCL8/CXCR2) are associated with clonal expansion and disease progression, notably SMF and leukemic transformation, and may explain the heterogeneity of disease [24-26]. DNMT3A and TET2 mutations appear to lead to the activation of inflammatory pathways, notably NF-κB signaling [27]. The activation of JAK/STAT leads to the clonal proliferation of megakaryocytes (MKs) in the BM where they are infiltrated by neutrophils and results in a "cyto-

kine storms", secreting a plethora of pro-inflammatory cytokines (IL-1β, TGF-β), and growth factors (b-FGF, PDGF, VEGF) [28]. This inflammatory BM microenvironment impacts the stability of the extracellular matrix and mesenchymal stromal cells, and ultimately stimulates fibrosis, angiogenesis and osteosclerosis [20]. JAK/STAT is also closely associated with fibrosis in a variety of tissues and organs, including the liver, renal, heart, and lung [29]. Such as the interaction of TGF-β and JAK/STAT pathways in renal/lung fibrosis and the activation of STAT3 in liver fibrosis [30-32].

STATs are a group of cytokine-driven transcription factors, so as to induce tumor immune escape, and modulate numerous proliferative aspects. Wu et al. reported that IL-6, IL-10, and VEGF can activate STAT3 and promote the development and recruitment of myeloid derived suppressor cells (MDSCs) [22]. MDSCs are major source of TGF-β and MMP, and then MDSCs regulate VEGF bioavailability and promote tumor angiogenesis. In addition, TGF-β can regulate MDSC function indirectly by altering microRNA expression [33]. We found that low levels of miR-146a recognize the risk of SMF progression by increasing STAT3 signaling [34]. STAT3 is also a potential candidate for TGF-β signal transduction. TGF-β induces lymphoma cells to produce IL-6 to activate STAT3, thereby activating the JAK/STAT signaling pathway.

NF-κB signaling

NF-κB represents a family that induces the expression of various pro-inflammatory genes, including tumor necrosis factor (TNF)-α, IL-6, IL-1β, TGF-β and CXCL8 (IL-8), and the crosstalk of NF-κB with other signaling pathways and the inflammasome is important [35]. Indeed, specific inflammatory cytokines such as IL-1β and IL-13 have recently been shown to be a major factor favoring JAK2V617F-mutated cells clonal expansion and MF in mouse models [36, 37]. The constitutive activation of NF-κB is one of the typical characteristics of activated B-cell (ABC) diffuse large B-cell lymphoma (DLBCL). Myeloid differentiation primary response gene 88 (MYD88) mutation, is present in 29% of patients with ABC-DLBCL, and it triggers the assembly of the active signaling complex composed of the IL-1 receptor-associated kinases IRAK1 and IRAK4. This results in IRAK4 kinase activation and IRAK1 phosphorylation, which promotes NF-κB signaling and induces lymphoma cells to produce IL-6 and IL-10. The autocrine action of IL-6 and IL-10 in turn activates JAK-STAT3 signaling [38, 39]. The expression of CXCLs may also play a role in DLBCL patients through the NF-κB signaling pathway, tumor-derived CXCL-8 promotes neutrophil infiltration, thereby providing a proliferation-inducing ligand (APRIL) in DLBCL [40]. Neutrophils have been reported to promote angiogenesis by their secretion of proangiogenic factors. The expression of β-TRCP1 promoted cell proliferation via TNF-dependent NF-κB activation in DLBCL cells [41]. Fisher et al. have shown that cytokine overproduction in MF is driven by TNF-α/NF-κB and MAP signaling pathways, as well as JAK-STAT [42]. The aberrant activation of the JAK-STAT pathway causes megakaryocytes to secrete b-FGF, TGF-β, PDGF, and VEGF, resulting in fibroblast proliferation, collagen deposition, and BM fibrosis.

Tumor microenvironment

The origins of MF-driving cytokines may vary. Some researchers believe they are secreted by lymphoma cells, while others speculate that they are derived from neighboring cells, such as monocytes. Thus, it is possible that cells residing adjacent to tumor cells play a major role in SMF pathogenesis. Few studies have characterized the tumor microenvironment (TME) of lymphoma patients with MF. The TME is a complex network of cellular and non-cellular components, including growth factors, pro-angiogenic factors, and adhesion molecules. Collectively, the components of the TME provide signals and favorable conditions for tumor cell survival and proliferation. Tumor-associated macrophages (TAMs) have been shown to promote tumor growth, invasion, and progression by generating angiogenic factors (e.g., VEGF, PDGF, TNF-α) and TGF-β [43]. Mesenchymal stem/stromal cells (MSC) also play a role in cancer development and progression (including in lymphoma) and MF [44]. Extracellular matrix (ECM) components in the BM of patients with lymphoma and PMF (including collagen, and laminin produced by megakaryocytes) also play an important role in MF [20]. TAMs have been shown to promote the development of human megakaryocytes; however, aberrant

mutant megakaryocytes aggravate fibrosis by secreting IL-1β, VEGF, TGF-β, b-FGF, and PDGF, perturbing angiogenesis, remodeling the ECM, and causing MSC dysfunction [20]. Megakaryocytes are a major source of TGF-β1, which can contribute to BM fibrosis. TGF-β1 induces the MSC proliferation, collagen synthesis, and JAK-STAT signaling pathway upregulation [45]. Meanwhile, the presence of FN1 in MSCs from MF patients has been shown to promote megakaryocyte differentiation and proliferation [46]. We found that they promoted and coordinated with each other. TGF-β activation also induces ECM remodeling and fibroblast transformation into myofibroblasts. Meanwhile, b-FGF controls the proliferation and function of diverse mesenchymal cells, increases angiogenesis and fibrosis in vivo, and induces the development of fibroblasts and endothelial cells in vitro [47]. In addition, PDGF stimulates the proliferation of BM fibroblasts and the production of reticular or collagen fibers by secreting collagen within a specific concentration range, thereby promoting BM fibrosis.

Cytokines

Currently most patients with a combination of lymphoma and MF occur in NHL, HL are exceedingly rare [48]. It has been documented, that elevated TGF-β, PDGF, and b-FGF expression have been reported in individuals with MF and hepatosplenic T-cell lymphoma (HSTL), angioimmunoblastic T-cell lymphomas (AITL), or peripheral T-Cell lymphoma (PTCL) [49-51]. In addition, NHL-SMF may also arise in BCLs such as follicular lymphoma (FL), intravascular large B-cell lymphoma (IVLBCL), chronic lymphocytic leukemia (CLL), and DLBCL [15, 52-54]. A few occur in HL, such as nodular sclerosing HL (NSHL). In our previous study of FL combined with MF, we found that the levels of cytokines such as b-FGF, TNF-α, TGF-β, PDGF, and IL-1β were reduced in lymphoma patients in remission, indicating that these cytokines may be play an important role in the occurrence of NHL associated with MF [15]. These cytokines may contribute to fibrosis development in this fraction of patients. TGFβ is over expressed and activated in fibrotic diseases, regulates fibroblast differentiation into myofibroblasts and induces abnormal and excessive accumulation of ECM constituents, particularly fibronectin, laminin, and collagens [55]. Activated fibroblasts, myofibroblasts, macrophages and epithelial cells represent an important source of TGF-β1 expression. TGF-β is also produced by platelets, neutrophils, and monocytes. The activation of TGF-β/Smad pathway upregulate transcription of ECM proteins and alpha smooth muscle actin (α-SMA), that marks myofibroblast differentiation. TGF-β also activates non-Smad signaling, notably the MAPK-AP1 pathways and P13K-Akt-mTOR signaling that contribute to fibrogenesis [56]. Additionally, increased protein expression in response to TGF-β is accompanied by attenuation of ECM protein degradation, e.g., through reduce matrix metalloproteinases (MMP) and enhanced expression of protease inhibitors. PDGF is mostly produced by hyperplastic MKs but can also be released by monocytes and macrophages. Recent work has demonstrated that PDGF is implicated in myelofibrosis [57]. Glioma-associated oncogene-1 (GLi1) and leptin receptor (LepR) MSC can differentiates into myofibroblasts that, LepR through PDGFRα/β-dependent signaling, enhances MSC proliferation, therefore enhancing the production of VEGF, secreting type I and III collagen, promoting the neovascularization, leading to MF [58]. As highlighted before, there is crosstalk between NF-κB and JAK-STAT signaling pathway. IL-6-activated STAT3 induces the expression of GLi1 and that STAT3-activated GLi1 contributes to the induction of BM fibrosis in MF [59]. Considering its role in fibroblast proliferation, b-FGF can have diverse effects on angiogenesis and, thus, MF [60]. IL-13 may also lead to fibrosis, and promote mast cell proliferation and infiltration. This in turn might produce the fibrotic cytokines IL-13 and TGF-β, resulting in HL fibrosis [61]. The findings presented suggest that the development of SMF in patients with lymphoma is tied to the abnormal activation of signaling pathways and the secretion of cytokines by lymphoma cells. By stimulating the proliferation of fibroblasts in the BM and increasing collagen synthesis, promote fibrosis, angiogenesis, and alter the BM microenvironment.

Conclusion

Most lymphomas are associated with SMF, while the combination of lymphoma and PMF is rare. Of the few studies investigating the pathogenesis of lymphoma complicated by MF, it is speculated that the pathogenesis of SMF

may be related to the abnormal activation of JAK-STAT signaling and the cytokines produced by lymphoma cells, such as TGF-β, PDGF, TNF-α, IL-1β, and b-FGF. These cytokines stimulate fibrous tissue proliferation and collagen synthesis in the BM, ultimately leading to MF. However, it is clear that MF is not the product of a single mechanism. Tumor microenvironment and other signaling pathways also contribute to lymphoma and MF pathogenesis. The conclusion of this review is that the mechanisms underlying the pathogenesis of lymphoma in association with MF need to be urgently clarified to improve the outcomes of patients with this combination of conditions.

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Disclosure of conflict of interest

None.

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