THE ROLE OF APOPTOSIS IN CHRONIC MYELOPROLIFERATIVE NEOPLASMS

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Abstract (Annotation)

Chronic myeloproliferative neoplasms (MPNs) are clonal hematologic disorders arising from hematopoietic stem cells and characterized by sustained proliferation of myeloid lineage cells. These diseases, including polycythemia vera, essential thrombocythemia, and primary myelofibrosis, are commonly associated with recurrent molecular abnormalities such as *JAK2*, *CALR*, and *MPL* mutations. While enhanced proliferative signaling is a defining feature of MPNs, increasing evidence highlights dysregulation of apoptosis as a key contributor to their pathogenesis.

Apoptosis is a tightly regulated biological process essential for maintaining hematopoietic homeostasis through the elimination of damaged or genetically unstable cells. In MPNs, impairment of intrinsic and extrinsic apoptotic pathways results in resistance to programmed cell death, promoting prolonged survival and accumulation of abnormal myeloid progenitor cells in the bone marrow and peripheral blood. Altered expression of critical apoptotic regulators, including upregulation of anti-apoptotic proteins and suppression of pro-apoptotic factors, plays a significant role in disease persistence, clinical heterogeneity, and progression to advanced disease stages.

This review summarizes the molecular mechanisms of apoptosis, outlines the major apoptotic alterations observed in chronic myeloproliferative neoplasms, and discusses their clinical and prognostic implications. Understanding apoptosis-related dysregulation in MPNs may facilitate improved risk stratification and support the development of targeted therapeutic strategies aimed at restoring programmed cell death in malignant hematopoietic cells

Keywords: apoptosis, chronic myeloproliferative neoplasms (MPNs), JAK2 mutation, cellular survival mechanisms, hematopoiesis, prognosis

Introduction to Apoptosis

Apoptosis is a highly regulated and genetically programmed form of cell death that plays a fundamental role in maintaining tissue homeostasis, controlling cell population dynamics, and eliminating damaged, senescent, or genetically altered cells in multicellular organisms. Unlike necrosis, apoptosis is an orderly and energy-

dependent process that prevents inflammatory responses and ensures physiological tissue remodeling. In the hematopoietic system, particularly within the bone marrow microenvironment, apoptosis is essential for regulating hematopoietic stem and progenitor cell turnover and preserving normal blood cell production.

The apoptotic process is orchestrated by a complex network of molecular signals involving the coordinated action of pro-apoptotic and anti-apoptotic proteins. Key pro-apoptotic factors include members of the BCL-2 family such as BAX and BAK, as well as cysteine-aspartic proteases known as caspases, which serve as central executioners of apoptosis. In contrast, anti-apoptotic proteins, including BCL-2, BCL-XL, and survivin, promote cell survival by inhibiting mitochondrial outer membrane permeabilization and suppressing caspase activation. The delicate balance between these opposing signals determines cellular fate.

Apoptosis is mediated through two principal pathways. The intrinsic (mitochondrial) pathway is activated in response to intracellular stress signals such as DNA damage, oxidative stress, or oncogene activation. This pathway involves mitochondrial cytochrome c release, formation of the apoptosome, and subsequent activation of initiator caspase-9, followed by executioner caspase-3. The extrinsic (death receptor) pathway, on the other hand, is initiated by extracellular ligands binding to specific death receptors on the cell surface, leading to caspase-8 activation and downstream apoptotic signaling.

Disruption of apoptotic signaling, particularly through overexpression of anti-apoptotic proteins or inhibition of caspase activity, results in delayed or blocked programmed cell death. Such dysregulation allows abnormal cells to escape physiological elimination, thereby contributing to pathological conditions, including hematologic malignancies. Consequently, intact apoptotic mechanisms are critical for preventing malignant transformation and maintaining normal hematopoietic function.

Role of Apoptosis in Chronic Myeloproliferative Neoplasms

Apoptosis plays a pivotal role in maintaining normal hematopoiesis by regulating cell survival and eliminating abnormal or genetically unstable cells. In chronic myeloproliferative neoplasms (MPNs), however, this tightly controlled process is profoundly disrupted, contributing to the pathogenesis, persistence, and progression of the disease. While increased proliferative signaling is a hallmark of MPNs, growing evidence indicates that impaired apoptotic mechanisms are equally critical in driving the abnormal expansion of myeloid cells.

One of the central features of MPNs is the development of resistance to programmed cell death. Genetic alterations commonly observed in these disorders, particularly mutations in *JAK2*, *CALR*, and *MPL*, lead to constitutive activation of intracellular signaling pathways such as JAK–STAT, PI3K–AKT, and MAPK. These pathways promote cell survival by upregulating anti-apoptotic proteins, including

BCL-2, BCL-XL, and survivin, while simultaneously suppressing pro-apoptotic factors such as BAX, BAK, and p53. As a result, malignant hematopoietic progenitor cells evade apoptosis and accumulate within the bone marrow and peripheral circulation.

Dysregulation of the intrinsic apoptotic pathway appears to be particularly significant in MPNs. Impaired mitochondrial signaling, reduced cytochrome c release, and decreased activation of initiator caspase-9 and executioner caspase-3 have been documented in neoplastic myeloid cells. This defective apoptotic response allows cells harboring DNA damage or oncogenic mutations to survive and continue proliferating, thereby sustaining clonal dominance. Additionally, alterations in the extrinsic apoptotic pathway, including reduced sensitivity to death receptor–mediated signals, further enhance apoptotic resistance.

The consequences of apoptotic dysregulation extend beyond abnormal cell accumulation. Resistance to apoptosis contributes to clinical manifestations such as splenomegaly, cytopenias due to marrow fibrosis, thrombotic complications, and increased risk of disease progression to acute myeloid leukemia. Moreover, the degree of apoptotic impairment has been associated with disease severity and prognosis, particularly in primary myelofibrosis.

Importantly, the central role of apoptosis in MPN biology has significant therapeutic implications. Targeted treatments, including JAK inhibitors, partially restore apoptotic signaling by suppressing aberrant survival pathways. Ongoing research into agents that directly target anti-apoptotic proteins holds promise for enhancing treatment efficacy and overcoming resistance.

In summary, defective apoptosis is a fundamental pathogenic mechanism in chronic myeloproliferative neoplasms, acting in concert with uncontrolled proliferation to drive disease development and progression. Understanding the molecular basis of apoptotic dysregulation in MPNs is essential for improving prognostic assessment and developing more effective, mechanism-based therapeutic strategies.

Clinical Implications and Therapeutic Targeting of Apoptosis in MPNs

The dysregulation of apoptosis in chronic myeloproliferative neoplasms (MPNs) has important clinical implications, influencing disease presentation, progression, prognosis, and response to therapy. Resistance to programmed cell death allows malignant hematopoietic clones to persist despite regulatory mechanisms that normally limit cell survival, thereby contributing to the chronic nature and clinical heterogeneity of MPNs.

From a prognostic perspective, alterations in apoptotic signaling pathways have been associated with disease severity and outcomes, particularly in advanced forms such as primary myelofibrosis. Increased expression of anti-apoptotic proteins, including BCL-2 family members and survivin, has been correlated with higher disease

burden, bone marrow fibrosis, splenomegaly, and reduced overall survival. Conversely, preservation of pro-apoptotic signaling appears to be associated with more indolent disease courses, suggesting that components of the apoptotic machinery may serve as potential prognostic biomarkers.

Therapeutically, targeting apoptotic resistance represents a promising strategy in the management of MPNs. Current standard treatments, such as Janus kinase (JAK) inhibitors, including ruxolitinib, primarily aim to suppress aberrant proliferative and inflammatory signaling driven by constitutive JAK–STAT pathway activation. In addition to symptom control and reduction of splenomegaly, these agents indirectly promote apoptosis by downregulating survival signals and decreasing the expression of anti-apoptotic proteins. However, JAK inhibition alone may not fully restore apoptotic sensitivity, highlighting the need for combination approaches.

Emerging therapeutic strategies focus on directly modulating apoptotic pathways. Small-molecule inhibitors targeting anti-apoptotic proteins, such as BCL-2 and related family members, have demonstrated pro-apoptotic effects in preclinical models and early clinical studies. These agents aim to shift the balance toward cell death in malignant clones while sparing normal hematopoietic cells. Additionally, therapies designed to enhance pro-apoptotic signaling or reactivate p53-mediated apoptosis are under investigation.

The integration of apoptosis-targeted therapies with existing treatment modalities may improve disease control, overcome therapeutic resistance, and potentially delay or prevent leukemic transformation. As molecular profiling becomes increasingly incorporated into clinical practice, individualized therapeutic strategies based on apoptotic pathway alterations may further optimize outcomes for patients with MPNs.

In conclusion, apoptotic dysregulation not only contributes to the pathogenesis of MPNs but also holds significant clinical and therapeutic relevance. Targeting apoptosis represents a rational and evolving approach that may enhance current treatment paradigms and improve long-term outcomes in patients with chronic myeloproliferative neoplasms.

Conclusion

Chronic myeloproliferative neoplasms represent complex clonal disorders of hematopoiesis in which abnormal cell proliferation is closely intertwined with impaired regulation of programmed cell death. While excessive activation of proliferative signaling pathways has long been recognized as a defining feature of MPNs, accumulating evidence indicates that dysregulation of apoptosis plays an equally critical role in disease initiation, persistence, and progression. Defective apoptotic mechanisms allow genetically altered myeloid progenitor cells to evade physiological elimination, resulting in their prolonged survival, clonal expansion, and accumulation within the bone marrow and peripheral blood.

Alterations in both intrinsic and extrinsic apoptotic pathways, particularly the imbalance between pro-apoptotic and anti-apoptotic regulators, contribute significantly to clinical heterogeneity and variable disease outcomes observed in MPN patients. Resistance to apoptosis not only underlies many of the characteristic clinical manifestations, such as splenomegaly, marrow fibrosis, and thrombotic complications, but also increases the risk of disease progression and leukemic transformation. Therefore, apoptotic dysregulation should be regarded as a fundamental pathogenic mechanism rather than a secondary phenomenon.

From a clinical perspective, improved understanding of apoptosis-related molecular abnormalities offers valuable opportunities for prognostic stratification and therapeutic innovation. Targeted therapies that modulate apoptotic pathways, particularly when combined with existing treatments, may enhance disease control and improve long-term outcomes. Continued research integrating molecular, clinical, and regional epidemiological data, including studies conducted in Uzbekistan, is essential for optimizing personalized management strategies for patients with chronic myeloproliferative neoplasms.

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