PATHOGENESIS AND ETIOLOGY OF CHRONIC MYELOPROLIFERATIVE NEOPLASMS (CMPNS): A COMPREHENSIVE REVIEW

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Abstract

Chronic myeloproliferative neoplasms (CMPNs) are a heterogeneous group of hematopoietic stem cell disorders characterized by the clonal proliferation of one or more myeloid lineages. The main subtypes include chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). These disorders share common pathogenic mechanisms, often involving mutations in genes such as JAK2, CALR, and MPL, leading to dysregulated signaling pathways and abnormal hematopoiesis. This review summarizes the current understanding of the etiology and pathogenesis of CMPNs, highlighting molecular mechanisms, clinical manifestations, diagnostic criteria, and potential therapeutic targets.

Keywords: Chronic myeloproliferative neoplasms, CMPNs, pathogenesis, etiology, JAK2 mutation, polycythemia vera, essential thrombocythemia, primary myelofibrosis, hematopoiesis

Introduction

Chronic myeloproliferative neoplasms (CMPNs) represent a group of clonal hematopoietic stem cell disorders characterized by the overproduction of mature blood cells. These diseases were first described in the mid-20th century and have since been recognized as distinct pathological entities based on clinical, hematological, and molecular features. CMPNs include chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).

The pathogenesis of CMPNs involves complex interactions between genetic mutations, aberrant signal transduction pathways, and the bone marrow microenvironment. Advances in molecular biology have elucidated key mutations that

drive these diseases, particularly those affecting the Janus kinase 2 (JAK2) gene, calreticulin (CALR), and the thrombopoietin receptor (MPL).

This article aims to provide a detailed overview of the etiology and pathogenesis of CMPNs, discussing each subtype's molecular mechanisms, clinical features, and implications for treatment.

1. Chronic Myeloid Leukemia (CML)

Etiology

Chronic myeloid leukemia is a clonal myeloproliferative disorder primarily caused by the reciprocal translocation between chromosomes 9 and 22, resulting in the formation of the Philadelphia chromosome (Ph). This translocation creates a fusion gene called **BCR-ABL1**, which encodes a constitutively active tyrosine kinase enzyme. The exact cause of this chromosomal abnormality is unknown, but it leads to uncontrolled proliferation of myeloid cells.

Pathogenesis

The BCR-ABL1 fusion protein continuously activates several signaling pathways, including the RAS/MAPK, PI3K/AKT, and JAK/STAT pathways. This abnormal signaling promotes cell proliferation, inhibits apoptosis, and disrupts normal differentiation of hematopoietic stem cells. The clonal expansion of these transformed cells leads to the characteristic leukocytosis seen in CML.

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2. Polycythemia Vera (PV)

Etiology

Polycythemia vera is characterized by an increased red blood cell mass and is strongly associated with a mutation in the **JAK2 gene (JAK2 V617F)** in over 95% of cases. This mutation leads to constitutive activation of the JAK-STAT signaling pathway. The precise trigger for the mutation remains unclear, but environmental and genetic factors may play a role.

Pathogenesis

The JAK2 V617F mutation causes hypersensitivity to growth factors such as erythropoietin, thrombopoietin, and granulocyte colony-stimulating factor. This results in autonomous erythrocytosis, leukocytosis, and thrombocytosis. The overproduction of blood cells increases blood viscosity, leading to a higher risk of thrombosis and other complications.

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- Essential Thrombocythemia (ET)
- Primary Myelofibrosis (PMF)
- **3. Essential Thrombocythemia (ET)**
- **Etiology**

- Essential thrombocythemia is characterized by the overproduction of platelets due to clonal proliferation of megakaryocytes. Similar to polycythemia vera, ET is frequently associated with mutations in the **JAK2 V617F** gene (~50-60% of cases), **CALR** (calreticulin) gene (~20-30%), or **MPL** (thrombopoietin receptor) gene (~5-10%). The exact cause of these mutations is not fully understood but may involve a combination of genetic predisposition and environmental factors.
- **Pathogenesis**
- Mutations in JAK2, CALR, or MPL result in constitutive activation of the JAK-STAT pathway, leading to uncontrolled proliferation of megakaryocytes and excessive platelet production. This abnormal signaling disrupts normal hematopoiesis and increases the risk of thrombotic and hemorrhagic events. The elevated platelet count can cause microvascular disturbances and complications related to abnormal clotting.
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- **4. Primary Myelofibrosis (PMF)**
- **Etiology**
- Primary myelofibrosis is a chronic myeloproliferative disorder characterized by progressive fibrosis of the bone marrow. Similar to ET and PV, mutations in **JAK2 V617F**, **CALR**, and **MPL** genes are commonly observed. Additional mutations affecting epigenetic regulators and splicing factors have also been identified, contributing to disease progression.
- **Pathogenesis**
- The mutated hematopoietic stem cells produce abnormal cytokines and growth factors, such as transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF), which stimulate fibroblast proliferation and collagen deposition in the bone marrow. This leads to marrow fibrosis, impaired hematopoiesis, extramedullary hematopoiesis (often in the spleen and liver), and progressive anemia and cytopenias. The aberrant JAK-STAT signaling further promotes clonal expansion and disease progression.

5. Diagnostic Approaches and Classification of CMPNs

Diagnostic Criteria

Diagnosis of chronic myeloproliferative neoplasms relies on a combination of clinical features, laboratory findings, bone marrow examination, and molecular genetic testing. The World Health Organization (WHO) criteria incorporate hematologic parameters, presence of specific mutations (JAK2, CALR, MPL), and bone marrow morphology.

- **Chronic Myeloid Leukemia (CML):** Detection of the Philadelphia chromosome (BCR-ABL1 fusion gene) via cytogenetics or PCR is diagnostic.

- **Polycythemia Vera (PV):** Elevated red cell mass, low erythropoietin levels, and presence of JAK2 mutation are key.
- **Essential Thrombocythemia (ET):** Persistent thrombocytosis with exclusion of reactive causes and detection of JAK2, CALR, or MPL mutations.
- **Primary Myelofibrosis (PMF):** Bone marrow fibrosis and clonal markers define the diagnosis.

Classification

CMPNs are classified based on clinical presentation, molecular abnormalities, and bone marrow pathology into:

- Chronic Myeloid Leukemia (CML)
- Polycythemia Vera (PV)
- Essential Thrombocythemia (ET)
- Primary Myelofibrosis (PMF)

Emerging subtypes and overlap syndromes are being studied to refine diagnosis and treatment.

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6. Therapeutic Perspectives (Brief Overview)

Treatment strategies depend on the specific CMPN subtype and disease stage. Targeted therapies such as tyrosine kinase inhibitors (TKIs) have revolutionized CML management by directly inhibiting the BCR-ABL1 kinase. JAK inhibitors like ruxolitinib have shown efficacy in PV and PMF by modulating aberrant JAK-STAT signaling.

Supportive treatments include phlebotomy in PV, cytoreductive therapy in ET, and hematopoietic stem cell transplantation in advanced PMF. Understanding the molecular pathogenesis has been crucial for developing these targeted approaches.

Conclusion

Chronic myeloproliferative neoplasms (CMPNs) represent a complex group of clonal hematopoietic stem cell disorders with diverse clinical presentations and molecular pathogenesis. The discovery of key mutations such as BCR-ABL1 in CML and JAK2, CALR, and MPL in other CMPNs has significantly advanced our understanding of these diseases. These mutations lead to dysregulated signaling pathways, resulting in uncontrolled proliferation and impaired differentiation of blood cells.

Improved diagnostic criteria incorporating molecular testing allow for precise classification and personalized treatment approaches. Targeted therapies, including tyrosine kinase inhibitors and JAK inhibitors, have transformed patient outcomes, especially in CML and other CMPNs.

Ongoing research into the molecular mechanisms and genetic landscape of CMPNs holds promise for novel therapeutic targets and improved management

strategies. Early diagnosis and understanding of pathogenesis remain critical for optimal patient care.

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