MOLECULAR GENETICS AND PATHOGENESIS OF CHRONIC MYELOPROLIFERATIVE NEOPLASMS: THE ROLES OF JAK2 V617F, CALR, MPL MUTATIONS, AND THE JAK-STAT PATHWAY

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Keywords: Chronic Myeloproliferative Neoplasms, JAK2 V617F, CALR Mutation, MPL Mutation, JAK-STAT Pathway, Molecular Pathogenesis, Myelofibrosis, Polycythemia Vera, Essential Thrombocythemia, Targeted Therapy.

Abstract: Chronic Myeloproliferative Neoplasms (MPNs) are clonal disorders of hematopoietic stem cells characterized by excessive proliferation of myeloid lineages. The pathogenesis of these disorders is closely associated with somatic mutations in genes that control intracellular signaling. Among these, mutations in **JAK2 (V617F)**, **CALR (Calreticulin)**, and **MPL (myeloproliferative leukemia virus oncogene)** are the most commonly implicated in BCR-ABL-negative MPNs. These mutations result in constitutive activation of the JAK-STAT pathway, leading to uncontrolled cell growth, survival, and cytokine hypersensitivity. Understanding these genetic alterations is essential for accurate diagnosis, prognosis, and treatment of MPNs. This article provides an in-depth review of the genetic mechanisms underlying MPNs, focusing on the roles of JAK2 V617F, CALR, MPL, and the JAK-STAT signaling pathway, and highlights current and emerging targeted therapies that are shaping modern clinical practice.

1. Introduction

Chronic Myeloproliferative Neoplasms (MPNs) are a group of clonal hematopoietic disorders characterized by excessive production of one or more mature blood cell types. MPNs primarily include **Polycythemia Vera (PV)**, **Essential Thrombocythemia (ET)**, and **Primary Myelofibrosis (PMF)**. Unlike acute leukemias, these diseases evolve slowly and can remain stable for years. However, they may eventually progress to myelofibrosis or transform into acute myeloid leukemia (AML), which is associated with poor prognosis.

The discovery of molecular mutations has revolutionized the understanding of MPNs. Approximately 95% of patients with PV and 50–60% of those with ET or PMF carry the JAK2 V617F mutation. In JAK2-negative cases, mutations in CALR or MPL are often found. These mutations are mutually exclusive and lead to persistent activation of JAK-STAT signaling, a pathway critical for cytokine signaling and hematopoiesis.

2. Overview of Chronic Myeloproliferative Neoplasms (MPNs)

2.1 Classification

According to the World Health Organization (WHO) classification, classic BCR-ABL-negative MPNs include:

- Polycythemia Vera (PV) – overproduction of red blood cells.
- Essential Thrombocythemia (ET) – elevated platelet counts.
- Primary Myelofibrosis (PMF) – marrow fibrosis and extramedullary hematopoiesis.

2.2 Pathophysiology

The hallmark of MPNs is constitutive signaling through pathways that regulate proliferation and survival. This results in cytokine hypersensitivity, increased cell turnover, bone marrow fibrosis, and increased thrombotic risk.

3. JAK2 V617F Mutation

3.1 Structure and Function of JAK2

JAK2 (Janus kinase 2) is a cytoplasmic tyrosine kinase involved in signaling downstream of cytokine receptors, such as the erythropoietin and thrombopoietin receptors. It plays a vital role in hematopoiesis.

3.2 The V617F Mutation

The V617F mutation is a valine-to-phenylalanine substitution at codon 617 in exon 14 of the JAK2 gene. This single-point mutation:

- Disrupts the autoinhibitory function of JAK2.
- Leads to constitutive kinase activity, independent of cytokine stimulation.
- Activates downstream STAT transcription factors.

3.3 Prevalence

- Found in ~95% of PV cases.
- Present in ~50–60% of ET and PMF patients.

3.4 Clinical Significance

- Associated with increased risk of thrombosis.
- Can be detected using allele-specific PCR, aiding diagnosis.
- Targeted by JAK inhibitors (e.g., ruxolitinib).

4. CALR (Calreticulin) Mutation

4.1 Function of CALR

Calreticulin (CALR) is a multifunctional calcium-binding protein in the endoplasmic reticulum involved in:

- Protein folding.
- Calcium homeostasis.
- Immune modulation.

4.2 CALR Mutations in MPNs

- Found in 20–25% of ET and PMF patients (especially JAK2-negative).
- Mutations are typically insertions or deletions in exon 9, leading to a frameshift.
- The mutant CALR protein gains oncogenic properties by interacting with the MPL receptor, activating JAK2 signaling.

4.3 Types of CALR Mutations

- Type 1: 52-bp deletion (L367fs*46)
- Type 2: 5-bp insertion (K385fs*47)

4.4 Clinical Features

- CALR-mutated MPNs often have:
  - Lower thrombotic risk than JAK2-mutated cases.
  - Better overall survival, especially in PMF.

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5. MPL (Myeloproliferative Leukemia Virus Oncogene) Mutation

5.1 Role of MPL

MPL encodes the thrombopoietin (TPO) receptor, crucial for megakaryocyte and platelet production.

5.2 Mutations

- Found in ~5–10% of ET and PMF cases.
- Common mutation: MPL W515L/K, affecting the juxtamembrane domain.
- Leads to ligand-independent activation of the receptor.

5.3 Pathogenic Mechanism

- Mutant MPL activates JAK2, which in turn activates STAT5.
- Promotes megakaryocyte proliferation and resistance to apoptosis.

5.4 Clinical Associations

- Associated with increased marrow fibrosis.
- Higher risk of progression to myelofibrosis.

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6. The JAK-STAT Signaling Pathway

6.1 Normal Function

- Activated by cytokines (e.g., EPO, TPO).

- JAK kinases phosphorylate STATs, which dimerize and move to the nucleus to regulate gene expression.

6.2 Aberrant Activation in MPNs

- JAK2 V617F, mutant CALR, and mutant MPL all result in constant JAK-STAT activation.
- This leads to:
  - Enhanced cell proliferation.
  - Cytokine hypersensitivity.
  - Chronic inflammation.

6.3 Key STAT Proteins

- STAT3 and STAT5 are particularly important in MPN pathogenesis.
- Regulate genes for survival (e.g., BCL-XL), proliferation (e.g., c-MYC), and cytokine signaling (e.g., SOCS3).

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7. Diagnostic and Prognostic Implications

7.1 Molecular Testing

- PCR and NGS-based tests for JAK2, CALR, and MPL mutations are routine in diagnosis.
- Mutation status influences:
  - Diagnostic criteria.
  - Risk stratification.
  - Choice of therapy.

7.2 Prognosis

- CALR mutations often confer a better prognosis than JAK2.
- Triple-negative (no JAK2, CALR, or MPL) MPNs have the worst outcomes.

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8. Therapeutic Approaches

8.1 JAK Inhibitors

- Ruxolitinib: A JAK1/2 inhibitor approved for myelofibrosis and hydroxyurea-resistant PV.
- Reduces spleen size and improves symptoms.
- Does not eliminate the malignant clone.

8.2 Future Therapies

- Fedratinib and Momelotinib: New JAK inhibitors with different profiles.
- CALR and MPL inhibitors are under investigation.
- Combination therapies (e.g., JAKi + interferon, epigenetic drugs) are being studied.

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9. Conclusion

Chronic Myeloproliferative Neoplasms are driven by key genetic mutations—JAK2 V617F, CALR, and MPL—that converge on the JAK-STAT signaling pathway. These mutations are not only central to disease development but also serve as important diagnostic and prognostic markers. Advances in molecular

📚 Key References

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