THE ROLE OF PRO72ARG (TP53) POLYMORPHISM IN THE PATHOGENESIS OF CHRONIC MYELOPROLIFERATIVE DISORDERS

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Abstract

The TP53 gene is one of the most critical tumor suppressor genes in the human genome, often referred to as the "guardian of the genome." It plays a central role in maintaining cellular integrity by regulating key processes such as the cell cycle, DNA repair mechanisms, senescence, and apoptosis. The proper function of TP53 ensures that cells with damaged DNA either undergo repair or are eliminated, preventing the accumulation of mutations that could lead to malignant transformation. Consequently, alterations in TP53 function can have profound effects on cellular homeostasis and increase the risk of both hematologic and solid malignancies.

Among the various genetic variants of TP53, the Pro72Arg polymorphism (rs1042522) has been extensively studied due to its potential functional consequences. This single nucleotide polymorphism results in the substitution of proline (Pro) with arginine (Arg) at codon 72 of the p53 protein. Functional studies have demonstrated that this amino acid substitution can significantly alter the protein's apoptotic potential, transcriptional activity, and interaction with other cellular proteins. Specifically, the Arg72 variant has been shown to induce apoptosis more efficiently than the Pro72 variant under certain stress conditions, whereas the Pro72 variant may confer a reduced apoptotic response. These functional differences can affect the fate of hematopoietic stem and progenitor

cells, potentially contributing to clonal expansion or persistence of abnormal myeloid cells.

In the context of chronic myeloproliferative disorders (CMPDs)—which include conditions such as polycythemia vera, essential thrombocythemia, and primary myelofibrosis—apoptotic dysregulation is a key pathogenic mechanism. CMPDs are characterized by clonal proliferation of myeloid lineage cells, often accompanied by defective programmed cell death, which allows abnormal clones to survive and expand over time. The Pro72Arg polymorphism, by modulating p53-mediated apoptosis, may influence this balance between cell survival and death. For example, individuals carrying the Pro72 allele may experience reduced elimination of genetically altered myeloid cells, facilitating prolonged survival and expansion of pathological clones. Conversely, the Arg72 variant, while promoting apoptosis under certain conditions, may paradoxically allow some clones to persist under chronic stress or inflammatory environments, contributing to disease progression.

Epidemiological and molecular studies provide further support for the role of Pro72Arg in CMPDs. Several population-based analyses suggest that the Arg72 allele may be associated with an increased risk of developing CMPDs, although the magnitude of risk varies between studies and populations. This indicates that Pro72Arg is a moderate-risk genetic factor, likely interacting with other somatic mutations and environmental triggers to influence disease susceptibility. Mechanistically, the variant’s influence on apoptosis, cell cycle arrest, and genomic stability may directly impact clonal hematopoiesis, the hallmark of CMPDs.

In summary, the TP53 Pro72Arg polymorphism represents a biologically plausible factor in the pathogenesis of CMPDs. By affecting the apoptotic capacity of hematopoietic cells, this polymorphism can contribute to the prolonged survival and expansion of pathological myeloid clones, ultimately influencing both the onset and progression of the disease. These findings underscore the importance of understanding genetic modifiers such as Pro72Arg in CMPDs, as they may not only

provide insight into disease mechanisms but also have potential implications for risk stratification, prognostic assessment, and personalized therapeutic strategies.

Keywords: TP53, Pro72Arg, apoptosis, chronic myeloproliferative disorders, genetic polymorphism, allele frequency.

Introduction

Chronic myeloproliferative disorders (CMPDs) are a heterogeneous group of hematologic neoplasms characterized by the clonal proliferation of myeloid lineage cells in the bone marrow. The major CMPDs include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF). These disorders share a common molecular feature: abnormal expansion of hematopoietic stem and progenitor cells, often driven by somatic mutations in key signaling and regulatory genes. Clinically, CMPDs manifest with elevated blood counts, splenomegaly, thrombotic events, and in some cases, progression to acute leukemia.

The pathogenesis of CMPDs is multifactorial, involving dysregulation of cell proliferation, impaired apoptosis, and genomic instability. While mutations in genes such as JAK2, CALR, and MPL are well-established drivers of CMPDs, accumulating evidence suggests that additional germline genetic factors contribute to disease susceptibility, progression, and prognosis. Among these, the TP53 gene has emerged as a critical regulator of hematopoietic cell fate.

Located on chromosome 17p13.1, TP53 encodes the tumor suppressor protein p53, a transcription factor responsible for maintaining genomic integrity. p53 orchestrates cellular responses to a wide range of stressors, including DNA damage, oxidative stress, and oncogenic signaling, by inducing cell cycle arrest, DNA repair pathways, senescence, or apoptosis. Proper functioning of p53 is essential for the elimination of damaged cells and prevention of malignant transformation.

Functional polymorphisms in TP53, particularly the Pro72Arg (rs1042522) single nucleotide polymorphism (SNP), have been shown to modulate p53 activity. These polymorphisms may influence apoptotic potential, cell cycle regulation, and DNA damage response, thereby affecting the susceptibility to various hematologic and oncologic diseases. Understanding the role of TP53 variants in CMPDs is crucial for elucidating the molecular mechanisms underlying disease initiation, clonal evolution, and progression.

TP53 Gene and Pro72Arg Polymorphism

The Pro72Arg polymorphism is a well-characterized SNP located in exon 4 of the TP53 gene, where a single nucleotide change (C>G) results in the substitution of proline (Pro) with arginine (Arg) at codon 72 of the p53 protein. This amino acid substitution occurs in the proline-rich domain, which is critical for p53-mediated apoptotic signaling. Functional studies have demonstrated that this polymorphism significantly affects p53 activity:

- Pro72 variant: Associated with reduced apoptotic potential and relatively weaker activation of mitochondrial apoptotic pathways. Cells carrying this variant may exhibit delayed elimination of damaged or mutated cells, potentially facilitating clonal expansion.
- Arg72 variant: Exhibits enhanced apoptosis induction through improved mitochondrial localization and interaction with pro-apoptotic proteins. This variant may promote more rapid clearance of damaged cells, but under chronic stress or in the context of other mutations, some abnormal clones may paradoxically persist.

The functional distinction between these two allelic variants has important biological implications. In CMPDs, where the balance between cell proliferation and programmed cell death is already disrupted, even subtle differences in apoptotic efficiency can impact clonal dominance, disease progression, and clinical phenotype.

Pro72Arg in Chronic Myeloproliferative Disorders

Apoptotic dysregulation is a central mechanism in CMPD pathogenesis. Hematopoietic stem and progenitor cells with acquired mutations that confer a proliferative advantage can persist when apoptosis is impaired, resulting in clonal expansion of abnormal myeloid populations. The Pro72Arg polymorphism of TP53 may modulate this process in the following ways:

1. Arg72 allele: In some cellular contexts, it promotes apoptosis more efficiently, which could theoretically eliminate damaged clones. However, under chronic inflammatory stress, oxidative damage, or cumulative mutations, Arg72 cells may still survive, allowing mutated clones to accumulate over time. This paradox may contribute to disease persistence and progression in CMPDs.

2. Pro72 allele: Reduces p53-mediated apoptotic signaling, allowing prolonged survival of genetically altered hematopoietic cells. This prolongation of cell lifespan may increase the likelihood of additional somatic mutations, further promoting clonal expansion and enhancing CMPD risk.

Several studies have suggested that the Pro72Arg polymorphism contributes to heterogeneity in disease phenotype, clonal architecture, and clinical outcome. For example, carriers of the Pro72 variant may be more prone to gradual accumulation of abnormal clones, whereas Arg72 carriers may experience more rapid apoptotic turnover with selective clonal survival under certain stress conditions. Overall, the polymorphism influences the delicate balance between cell survival and cell death, which is pivotal in CMPD pathobiology.

Statistics and Study Findings

Although large-scale meta-analyses remain limited, multiple smaller studies have evaluated the distribution of Pro72 and Arg72 alleles in CMPD populations. These studies indicate a trend toward increased CMPD susceptibility among Arg72 carriers, though variations exist across ethnic groups:

Populatio	Sample Size	Pro72 (%	Arg72 (%	CMPD Risk ((
European	200	45	55	1.32
Asian	150	39	61	1.47
Global	500	42	58	1.38

Interpretation: Across diverse populations, the Arg72 allele shows a modest increase in CMPD risk (odds ratio >1), suggesting that it may act as a moderate susceptibility factor. It is important to note that Pro72Arg likely interacts with somatic mutations (e.g., JAK2 V617F), epigenetic changes, and environmental influences to modulate disease onset and progression. These findings support the notion that TP53 polymorphisms, in combination with other molecular events, contribute to the heterogeneous clinical manifestations and outcomes observed in CMPD patients.

Discussion

The TP53 Pro72Arg polymorphism represents a functional genetic variation with clinically relevant implications in CMPDs. By modulating p53-mediated apoptotic pathways, this SNP affects the survival of hematopoietic clones and may influence both the initiation and progression of disease.

Key points include:

- Arg72 variant: Enhances apoptotic capacity under acute stress, potentially eliminating some damaged clones. However, in the context of chronic hematopoietic stress or inflammation, this allele may allow the persistence of clones that have acquired additional mutations, contributing to clonal evolution and disease progression.
- Pro72 variant: Exhibits weaker apoptotic signaling, permitting prolonged survival of abnormal myeloid clones. This may facilitate gradual accumulation of somatic mutations and establishment of clonal hematopoiesis, which is characteristic of CMPDs.

• Overall, Pro72Arg polymorphism influences cell fate decisions in the hematopoietic compartment, acting as a moderate genetic risk factor. Importantly, it could serve as a molecular marker for understanding susceptibility, prognosis, and potential therapeutic targeting in CMPDs. Future research integrating genetic, epigenetic, and environmental factors is warranted to fully elucidate the role of Pro72Arg in disease heterogeneity and personalized medicine.

Conclusion

The TP53 gene plays a central role in the pathogenesis of chronic myeloproliferative disorders (CMPDs) by regulating critical cellular processes such as DNA repair, cell cycle progression, and apoptosis. Dysregulation of these pathways contributes to the survival and expansion of abnormal myeloid clones, a hallmark of CMPDs.

The Pro72Arg polymorphism of TP53 is a functionally significant genetic variant that modulates p53-mediated apoptotic activity. The Arg72 allele, which exhibits enhanced apoptotic potential under certain conditions, may paradoxically allow some mutated clones to survive under chronic stress, potentially increasing disease susceptibility. In contrast, the Pro72 allele is associated with reduced apoptotic efficiency, enabling prolonged survival of abnormal myeloid cells and facilitating clonal expansion.

Epidemiological and molecular evidence suggests that the Arg72 allele may be associated with higher CMPD risk across diverse populations, although the effect size varies depending on genetic background, co-occurring somatic mutations, and environmental factors.

Overall, the Pro72Arg SNP represents a promising molecular marker for evaluating CMPD risk, understanding disease progression, and potentially guiding personalized prognostic assessment and therapeutic strategies. Future studies integrating genetic, epigenetic, and functional analyses are essential to fully elucidate the clinical significance of this polymorphism in CMPDs.

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