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ROLE OF TNF-A PROMOTER POLYMORPHISM G308A IN CHRONIC MYELOPROLIFERATIVE NEOPLASMS: MOLECULAR MECHANISMS, CLINICAL IMPLICATIONS, AND FUTURE PERSPECTIVES

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Abstract: *Myeloproliferative neoplasms (MPNs) are clonal hematopoietic stem cell disorders characterized by excessive proliferation of one or more myeloid lineages. Inflammation and cytokine dysregulation are increasingly recognized as key contributors to disease initiation, progression, and phenotypic heterogeneity in MPNs. Tumor necrosis factor-alpha (TNF-α) is a central proinflammatory cytokine whose expression is regulated at the transcriptional level, in part via promoter polymorphisms such as the G→A substitution at position –308 (commonly called G308A, or rs1800629). The G308A polymorphism has been investigated in various inflammatory, oncologic, and hematologic disorders, but its specific role in MPNs remains underexplored. In this review, we summarize current knowledge of TNF-α function in hematopoiesis and MPN pathophysiology, examine available evidence regarding the G308A polymorphism in hematologic and neoplastic diseases, propose mechanistic models for how the G308A variant might influence MPN phenotypes, and outline experimental and clinical strategies to test its relevance. We conclude that although direct data are scarce, the G308A polymorphism represents a plausible modulatory factor in MPNs, with potential value as a biomarker or therapeutic target, warranting deeper investigation.*

Keywords: *TNF-α, G308A polymorphism, myeloproliferative neoplasms, inflammation, cytokine regulation, clonal hematopoiesis, biomarker, promoter polymorphism.*

1. Introduction

- **Overview of Myeloproliferative Neoplasms (MPNs).**

Myeloproliferative neoplasms (MPNs) are a group of clonal hematopoietic stem cell disorders characterized by overproduction of one or more myeloid cell lineages (erythrocytes, granulocytes, megakaryocytes) in the bone marrow, often with extramedullary hematopoiesis, splenomegaly, and risk of progression to myelofibrosis or acute leukemia. Википедия+2Wiley Online Library+2

Common driver mutations include **JAK2 V617F**, **CALR** (calreticulin) indels, and **MPL** mutations, which activate the JAK–STAT signaling pathway. Wiley Online Library+1 Despite these well-known drivers, disease heterogeneity (for example, differences in symptom burden, progression, thrombosis risk) suggests that additional modifiers—including inflammatory mediators and germline variants—play roles in disease phenotype and evolution.

- **Inflammation, cytokines, and the hematopoietic niche in MPNs.**

Chronic, nonresolving inflammation is a hallmark of MPNs; patients frequently experience constitutional symptoms (fatigue, weight loss, fever), elevated inflammatory markers (CRP, IL-6, TNF-α), and an inflammatory bone marrow microenvironment. PubMed+2Wiley Online Library+2

Cytokines such as TNF-α may influence both the malignant clone and nonclonal hematopoiesis, modulating competition, survival, apoptosis, and microenvironment interactions. Indeed, evidence indicates that TNF-α can preferentially suppress normal progenitors while supporting or permitting clonal expansion of mutant cells (e.g. JAK2 V617F–bearing). PubMed

Given that TNF-α levels are regulated (in part) by promoter variants in the TNFA gene, the presence of polymorphisms such as G308A might modulate individual susceptibility to MPN development, clonal dominance, or disease progression.

- **Rationale for focusing on TNF-α G308A polymorphism.**

The **–308 G → A** polymorphism (rs1800629) in the promoter region of the TNFA gene is among the most studied functional variants of TNF-α. It is known to influence transcriptional activity of the TNFA promoter, with the A allele often associated with increased transcription and elevated TNF-α expression in various

contexts. This variant has been evaluated in multiple inflammatory, autoimmune, infectious, and oncologic conditions, with varying results. However, there is limited direct evidence in MPNs, and mechanistic implications remain largely speculative. Thus, a focused review is warranted to (i) consolidate what is known about G308A in related hematologic diseases, (ii) consider mechanistic models in MPN contexts, and (iii) propose directions for future study.

2. TNF-α: Biology, Regulation, and Role in Hematopoiesis

2.1 Structure and function of TNF-α

- TNF-α (tumor necrosis factor–alpha) is a pivotal proinflammatory cytokine involved in immune regulation, cell survival, apoptosis, and inflammatory signaling pathways (e.g. NF-κB, MAPK).
- It is produced primarily by monocytes/macrophages, but also by T cells, natural killer cells, and other stromal cells under certain stimuli.
- TNF-α exerts effects via binding to two major receptors, **TNFR1 (p55, TNFRSF1A)** and **TNFR2 (p75, TNFRSF1B)**, which trigger downstream signaling pathways including NF-κB and MAPKs, leading to transcription of inflammatory genes, cell survival, or apoptosis depending on context.

2.2 Transcriptional regulation and promoter polymorphisms

- The transcriptional activity of TNFA is tightly regulated by promoter elements, including binding sites for NF-κB, SP1, AP-1, and other transcription factors.
- The **–308 G → A** polymorphism lies upstream of the transcription start site and may influence binding of transcription factors, chromatin structure, or promoter strength.
- Some functional studies (in non-hematologic contexts) have shown that the A allele is associated with higher promoter activity and elevated TNF-α mRNA or protein levels compared to the G allele, though the effect can be context- and cell-type dependent.

2.3 TNF-α in hematopoiesis and clonal dynamics

- TNF-α has complex effects on hematopoietic stem and progenitor cells (HSPCs): at high concentrations, TNF-α can suppress hematopoiesis, induce apoptosis, or inhibit proliferation of certain progenitors.
- In a clonal context, cells harboring oncogenic mutations (e.g., JAK2 V617F) may acquire resistance or even proliferative advantage in the presence of TNF-α, whereas normal (wild-type) progenitors are more sensitive to its inhibitory/apoptotic effects. Indeed, an important experimental observation in an MPN model shows that JAK2 V617F–positive progenitors resist suppression by TNF-α and may expand preferentially under TNF-α–rich conditions. PubMed
- In vivo, genetic or pharmacologic suppression of TNF-α in murine MPN models has been shown to limit clonal expansion and attenuate disease, supporting the notion that TNF-α is not merely a bystander but a driver of clonal selection. PubMed+1
- Further, differential signaling via TNFR1 versus TNFR2 may differentially influence inflammation, apoptosis, or proliferation in the MPN niche. Anti–TNFR1 or anti–TNFR2 therapies have been proposed as potential adjuncts to JAK inhibitors in MPN models. PubMed

3. The TNF-α G308A (rs1800629) Polymorphism: Evidence from Hematologic and Related Disorders

Because direct studies of G308A in MPNs are rare or absent, we must draw on related hematologic, neoplastic, and inflammatory disease literature and meta-analyses to infer potential relevance.

3.1 Evidence in myelodysplastic syndromes (MDS) and related disorders

- A recent meta-analysis of eight studies (1,180 MDS cases, 1,387 controls) found that the **G allele** (vs A) of the G308A variant was associated with **decreased MDS susceptibility** under multiple genetic models (allelic, homozygote, recessive). PubMed
- In particular, the **GG genotype** was associated with lower risk of MDS compared to GA (OR, P-values significant). PubMed+1

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- The authors suggest that the A allele (associated with higher TNF-α expression) might create a proinflammatory/hematopoietic stress environment that predisposes to dysplasia or clonal selection. PubMed+1
- Another meta-analysis focusing on TNF-α polymorphisms (including G308A) in MDS also supported associations between genotypes and susceptibility, though emphasizing heterogeneity and need for further study. Tandfonline
- These findings implicate that G308A may modulate risk of clonal hematopoietic disorders, and by analogy, could influence MPN risk or phenotype.

3.2 Evidence in other hematologic malignancies and immune disorders

- In acute lymphoblastic leukemia (ALL), the A allele of G308A was found to correlate with poorer prognostic factors (e.g., older age, extramedullary disease, relapse rate), possibly via elevated TNF-α production. Lippincott
- Studies in autoimmune, inflammatory, and infectious diseases often report associations between the A allele and increased disease risk or severity, e.g. chronic hepatitis C, though results are heterogeneous. BioMed Central
- In analyses of essential hypertension (not hematologic but inflammatory/injury milieu), a meta-analysis showed that the G308A polymorphism was associated with hypertension risk in certain genetic models (A allele being risk allele). Наццентр биотехинформации
- Overall, the G308A polymorphism is biologically plausible as a modulator of inflammatory and proliferative responses, but disease-specific effects vary by context, cell type, and interacting variants.

3.3 Limitations of existing data and gaps

- No published study (to current knowledge) directly examines the TNF-α G308A variant in cohorts of MPN patients (e.g. polycythemia vera, essential thrombocythemia, primary myelofibrosis) and correlates genotype with clinical outcomes, allele burden, or cytokine levels.
- Many existing studies are case–control in design and may lack functional validation (i.e. measuring TNF-α levels by genotype).

- Ethnic heterogeneity, small sample sizes, and lack of stratification by relevant driver mutations (e.g. JAK2, CALR) limit interpretability.
- The effect of G308A likely interacts with many other genetic, epigenetic, and environmental factors; hence its individual effect size might be modest.

4. Proposed Mechanistic Models in the Context of MPNs

Given what we know about MPN biology and TNF-α's role in clonal selection, one can posit several mechanistic hypotheses by which G308A might modulate MPN initiation, progression, or phenotype.

4.1 Model A: Enhanced TNF-α expression fosters selective advantage for mutant clones

- In individuals carrying the **A allele**, baseline or induced TNF-α expression may be somewhat higher in the hematopoietic/stromal compartment.
- Under such conditions, normal (wild-type) HSPCs may be more susceptible to TNF-α–mediated apoptosis or growth suppression, whereas mutant clones (e.g. JAK2 V617F) may resist these effects or even benefit (as shown in experimental models). PubMed
- Thus, the A allele may lower the threshold for clonal expansion or help early mutant clones gain dominance.

4.2 Model B: Interaction with driver mutations and allele burden

- The influence of G308A may depend on the **driver mutation** (JAK2, CALR, MPL) and on the **allele burden** (proportion of hematopoietic cells carrying the mutation).
- For example, in early-stage disease with low allele burden, increased TNF-α (A allele) may accelerate clonal dominance; in later stages, effects may saturate or be masked by other factors.
- Alternatively, the presence of A allele could modulate the effect of therapeutic cytokine milieu, e.g. JAK inhibitor therapy combined with anti-inflammatory interventions.

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4.3 Model C: Modulation of microenvironment, stromal niche, and inflammation

- Elevated TNF-α in A-allele carriers may intensify inflammatory signaling in the bone marrow niche—leading to stromal activation, endothelial changes, fibrosis, and altered cytokine gradients.
- This microenvironment may favor survival or migration of mutant clones, or contribute to progression to myelofibrosis.
- Moreover, TNF-α can induce other downstream cytokines (IL-6, IL-1, etc.), generating a pro-proliferative milieu.

4.4 Model D: Influence on disease phenotype, complications, and progression

- Depending on the net balance of pro-proliferative versus suppressive effects, G308A may influence phenotypic distinctions: e.g. more splenomegaly, higher symptom burden, greater risk of transformation, or differential response to anti-inflammatory therapy.
- For example, A-allele carriers might show more constitutional symptoms or inflammatory features.

5. Experimental and Clinical Strategies to Test G308A in MPNs

To validate the above hypotheses and assess the clinical relevance of the G308A polymorphism in MPNs, the following approaches are recommended:

5.1 Genetic epidemiology / association studies

- **Case–control studies** in well-characterized MPN cohorts (PV, ET, MF) and matched healthy controls to assess genotype frequencies, allele distributions, and associations with disease risk.
- **Genotype–phenotype correlation** within MPN cohorts: stratify patients by G308A genotype (GG, GA, AA) and compare clinical variables (age at diagnosis, blood counts, symptom scores, splenomegaly, allele burden, thrombosis risk, transformation rates).
- **Cohort / prospective studies** to assess whether genotype predicts progression, survival, or response to therapy.

5.2 Functional assays

- **Cytokine measurement:** measure TNF-α mRNA and protein (plasma, bone marrow supernatant, cellular) in MPN patients stratified by genotype to test whether A allele carriers indeed express more TNF-α.
- **Promoter reporter assays:** construct TNFA promoter luciferase reporters containing –308 G or A alleles, and transfect into relevant hematopoietic/stromal cell lines to measure differential promoter activity in basal and stimulated conditions (e.g., under inflammatory stimuli).
- **Hematopoietic progenitor assays:** culture HSPCs (wild-type and mutant) in presence of varying TNF-α levels, compare proliferation/apoptosis by genotype context.
- **CRISPR/Cas9 editing** of cell lines to introduce G308A variant, then assess changes in expression and phenotype under stress/inflammatory conditions.

5.3 Animal models

- Generate **knock-in mouse models** bearing the human TNFA promoter with G or A allele, crossed with MPN models (e.g., JAK2 V617F) to assess impact of promoter variant on clonal expansion, disease severity, and progression under controlled conditions.
- Use **neutralizing antibodies or inhibitors** targeting TNFα, TNFR1, or TNFR2 in mice stratified by genotype to explore differential therapeutic response. (Some work has already been done with anti-TNFR1/2 in JAK2-V617F models) PubMed

5.4 Integration with multi-omics and bioinformatics

- **eQTL analysis:** use publicly available expression quantitative trait loci (eQTL) databases to check whether rs1800629 is associated with TNFA gene expression in hematopoietic tissues or peripheral blood.
- **Transcriptomic / proteomic profiling** of MPN samples stratified by G308A genotype to identify downstream effectors, pathway differences, or inflammatory signatures.

- **Gene–gene / haplotype interaction studies:** explore interactions between G308A and other germline variants (e.g. inflammatory gene SNPs) or with driver mutation allelic burden (e.g. JAK2 46/1 haplotype).

5.5 Clinical translation and biomarker development

- If associations are confirmed, G308A genotype may serve as a **biomarker** for risk stratification, prognostication, or therapeutic tailoring (e.g. selecting patients for adjunct anti-inflammatory therapy).
- Assess whether **anti-TNF or anti-TNF receptor therapies** have differential efficacy or safety in patients stratified by genotype in MPN clinical trials (in combination with JAK inhibitors).
- Evaluate **gene–environment interactions**, e.g. whether genotype modifies response to lifestyle or anti-inflammatory interventions (e.g. statins, anti-cytokine therapies).

6. Potential Clinical Implications and Challenges

- If G308A influences MPN behavior, genotype testing (germline) might help in **risk stratification**, **predicting progression**, or **tailoring adjunctive therapies**.
- However, the effect size of a single polymorphism is likely modest, so it should be integrated into polygenic risk scores or combined biomarker panels.
- Ethical and logistic challenges include ensuring adequate sample sizes, diverse populations, robust statistical correction for multiple testing, and functional validation.
- Because TNF-α is a pleiotropic cytokine with systemic effects, manipulating it (e.g. via inhibitors) carries risks (e.g. immune suppression, infection). Genotype-based selection might help mitigate such risks.

7. Conclusion and Future Directions

Although direct evidence is lacking, the **TNF-α promoter G308A (rs1800629)** polymorphism represents a biologically plausible modulator of inflammation and clonal dynamics in MPNs. The existing evidence from related hematologic disorders (such as MDS) and experimental models (demonstrating

TNF-α's role in promoting JAK2 V617F clone expansion) provides a compelling rationale to investigate this variant in MPN cohorts.

Key next steps include:

1. **Genotyping MPN patient cohorts** and correlating with clinical phenotype, progression, and response.
2. **Functional validation** of promoter activity, cytokine expression, and cellular phenotypes by genotype.
3. **Integration into multi-omic analyses** to map downstream pathways and interactions.
4. **Preclinical model studies** to test genotype-conditional effects and therapeutic modulation.
5. **Clinical trials** that may consider genotype stratification in adjunctive anti-inflammatory or anti–TNF strategies.

A comprehensive multi-disciplinary approach combining genetic epidemiology, molecular biology, hematology, and translational therapeutics is required. If validated, the G308A polymorphism could enrich our understanding of the inflammatory underpinnings of MPNs and contribute to personalized management.

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