9° WORKSHOP IN EMATOLOGIA TRASLAZIONALE

DELLA SOCIETÀ ITALIANA DI EMATOLOGIA SPERIMENTALE

Bologna, Aula "G. Prodi", 19-20 maggio 2025

Interazione tra coagulazione e infiammazione nelle neoplasie mieloproliferative croniche

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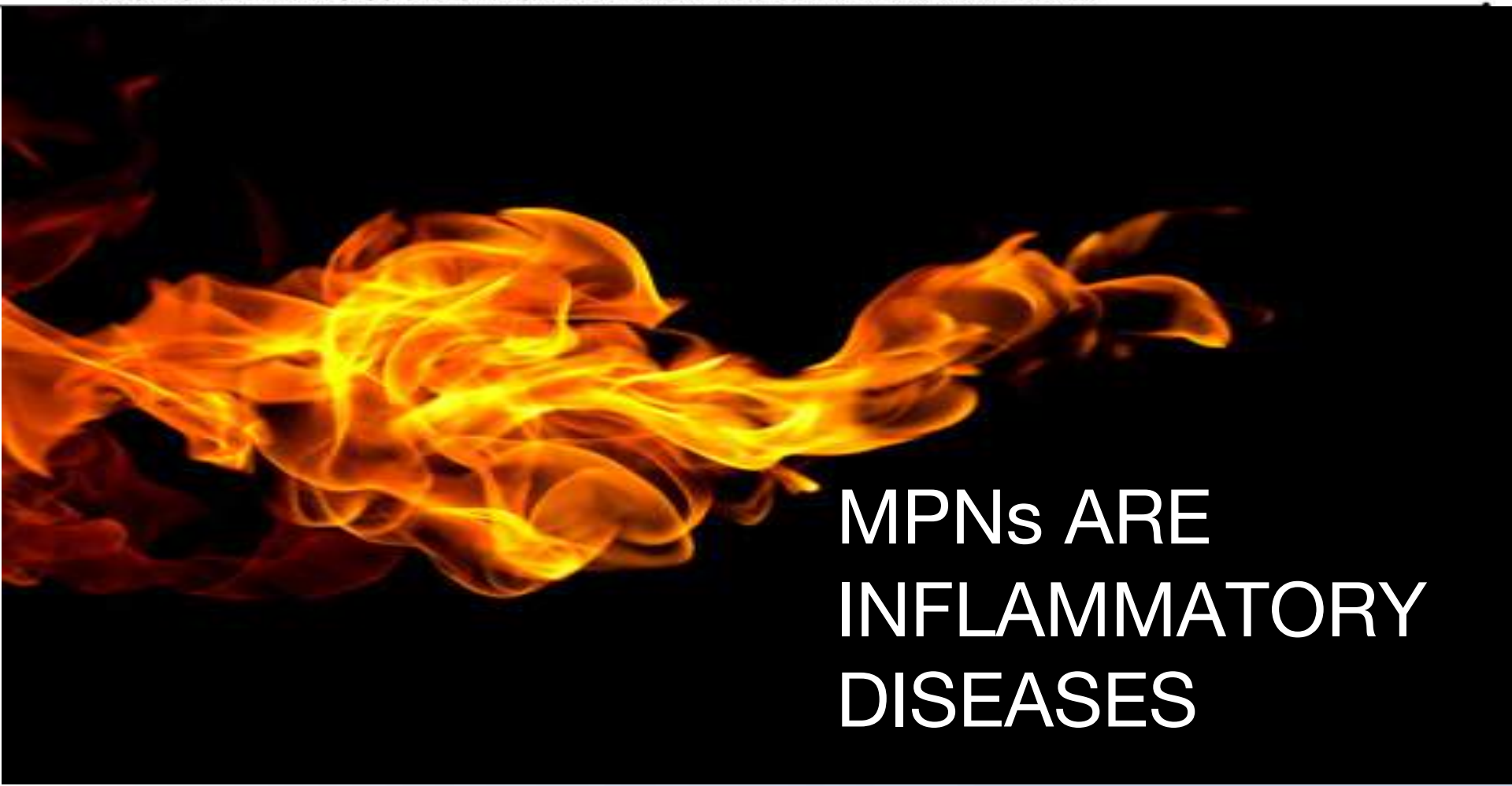
Disclosures di Nome Cognome

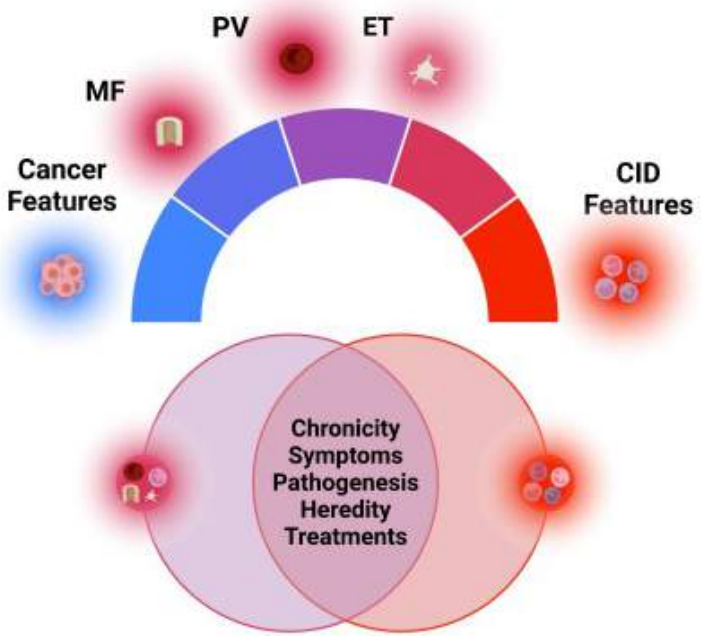
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
NOVARTIS			x		x	x	
GSK			x		x	x	
AOP			x		x	x	

1. MPNs are inflammatory diseases
2. Inflammation impacts on hemostasis
3. Role of NETs in MPN thrombosis
4. Thrombotic risk and inflammation in MPNs
5. Anti-inflammatory effect of anti-thrombotic and cytoreductive treatment
6. Anti-thrombotic effect of anti-inflammatory treatment



MPNs ARE INFLAMMATORY DISEASES

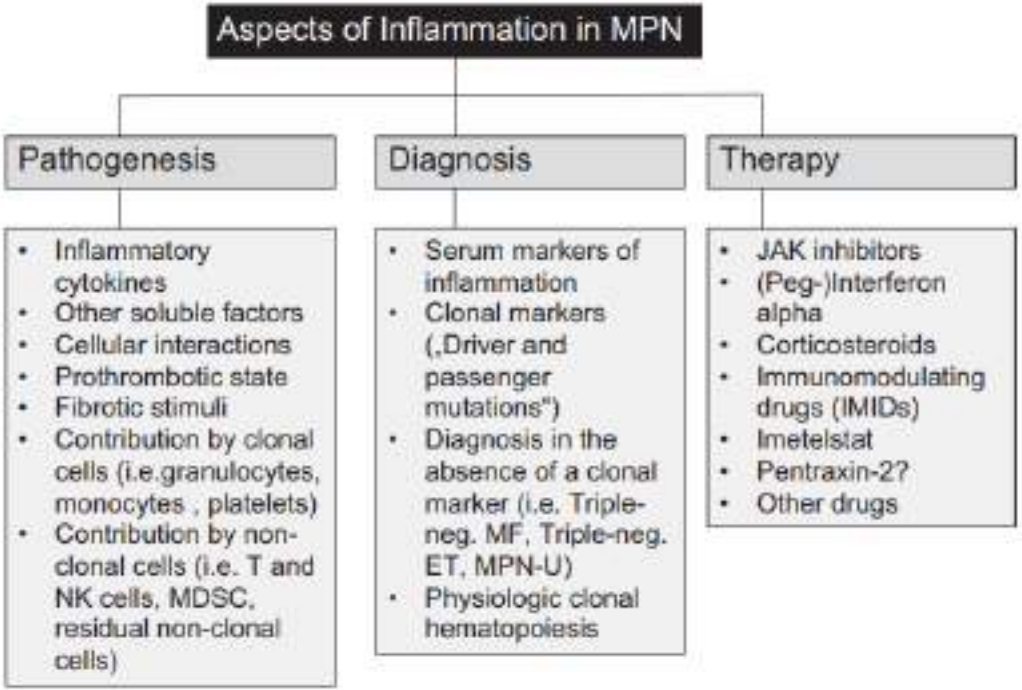
Chronic inflammation is a hallmark feature of MPN, most notably PMF, which plays an integral role in multiple aspects of its pathobiology, including symptomatology, thrombosis, disease progression, and heightened cardiovascular disease risk. Although MPN is currently classified as a malignancy, many of the aspects of the disease are more like a chronic inflammatory condition rather than a cancer.



Soyfer EM & Fleischman AG Front Oncol 2023

The chronic inflammation in MPNs has been described as a pivot for the development and advancement of MPNs **from early stage cancer to pronounced bone marrow fibrosis,** which may allow for the neoplastic clone to gain a selective advantage over unmutated wild-type cells.

We have still not resolved the issue of whether inflammation-related biological markers and clinical symptoms observed in MPN patients **can complement, or succeed, or even precede the acquisition of key mutations harbored by MPN clones.**



Koschmieder S et al. Leukemia 2016; Marković DC et al. Int J Mol Sci. 2023

About 79 kinds of cytokines have been evaluated at least once, and particularly **12 of the 79 cytokines could be prognostic factors for MPN patients** (IL-1α, **IL-1β**, IL-2Ra, IL-6, IL-8, IL-11, IFN, **TNF-α**, TGF-β, VEGF, PDGF and MIP-1).

TNF correla con burden di JAK2 V617F

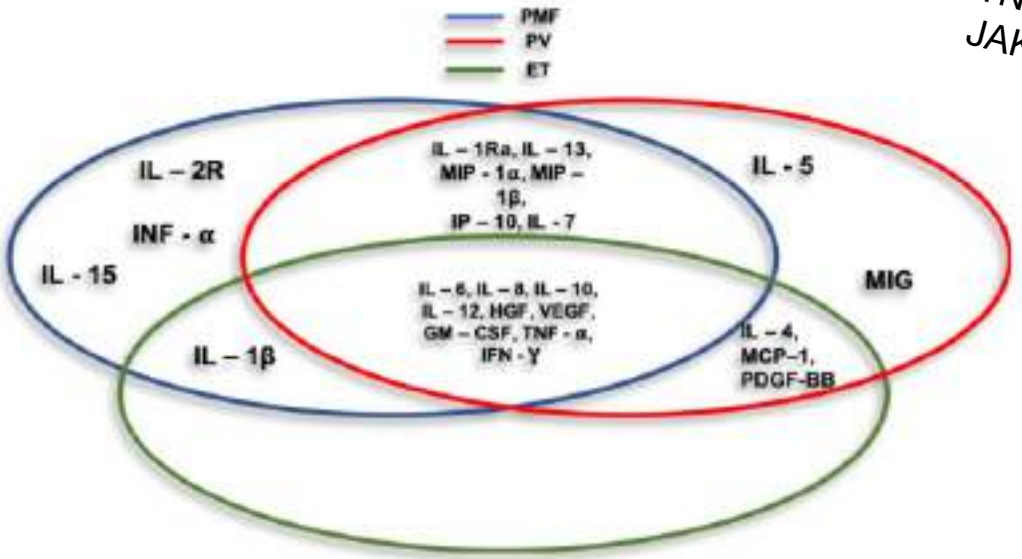


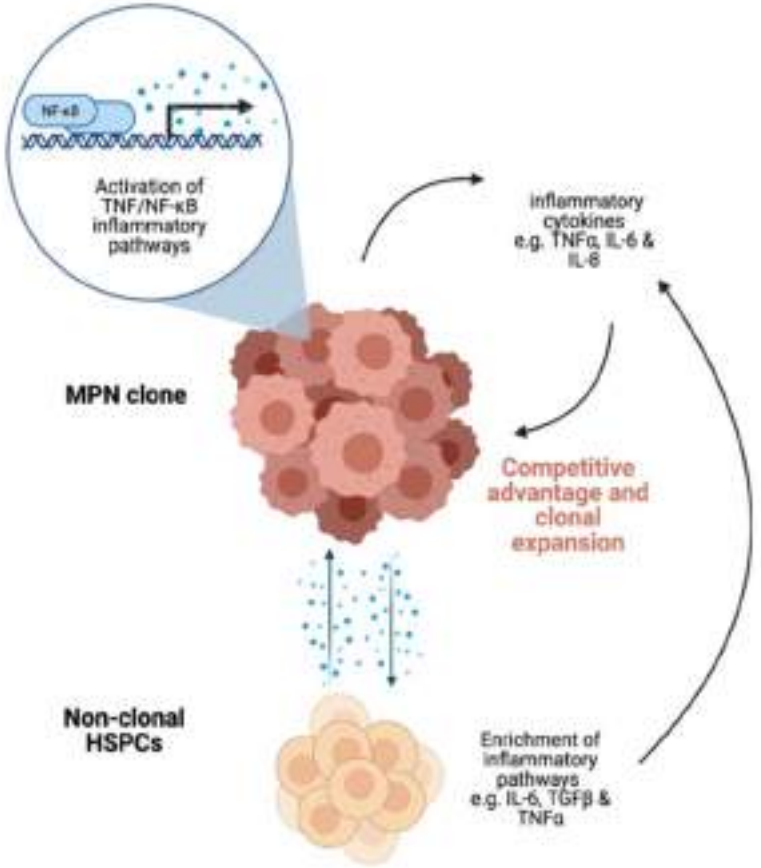
Figure 3. Cycles represent cytokines and chemokines associated with myeloproliferative neoplasms (MPNs) main entities.

Longhitano L et al. J Clin Med 2020, Wang Y et al Cytokine X 2019

Malignant hematopoietic cells create a chronically inflamed microenvironment via secretion of proinflammatory cytokines that severely disrupts the normal bone marrow niche.

Certain inflammatory cytokines that are increased in patients with MPN, including TNFa and IFNa, have been shown **to confer a selective growth advantage** to JAK2V617F-mutant over wild-type cells in vitro, enabling clonal expansion.

Furthermore, **MPN cells were found to stimulate nonmalignant cells to sustain the myeloproliferative disease** and they change the microenvironment in the BM by promoting the growth of the other MPN cells but suppressing the growth of normal cells, mostly by **autocrine and paracrine production of inflammatory cytokines.**



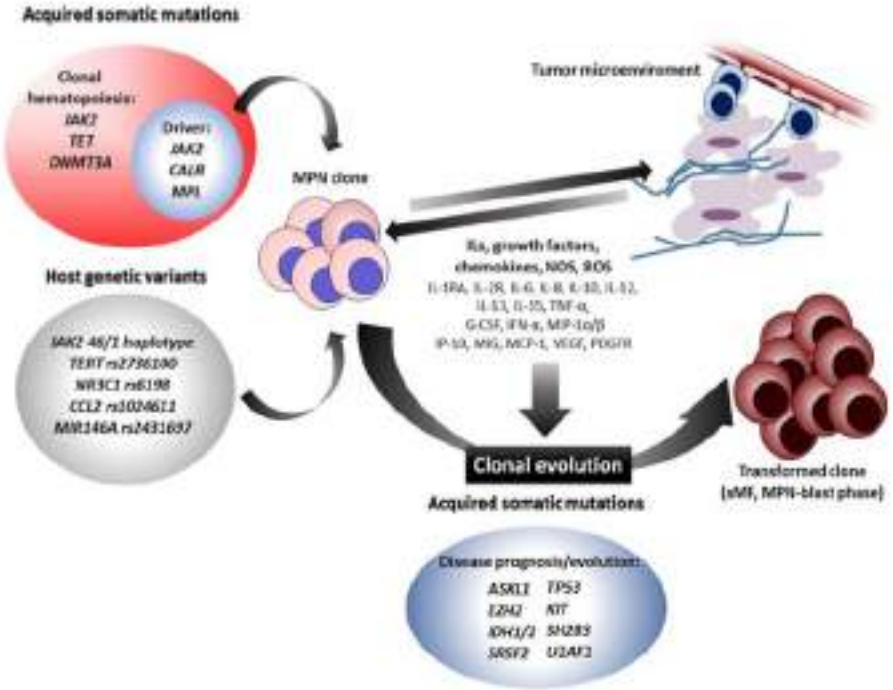
Koschmieder S et al. Leukemia 2016, Strickland M et al. BJH 2021

MPN patients can be considered **«dysfunctional cytokine producers».**

The malignant clone is at the same time the main source and the target of a cytokine storm acting both at a local and a sistemic level.

At a local level, cytokines induce changes to the tumor microenvironment (i.e., the bone marrow) eventually leading to **fibrosis,** which can be considered **as bone marrow end-organ damage**.

Systemic manifestations include constitutional symptoms, pro-thrombotic state, increased susceptibility to second cancers, and autoimmune disorders.

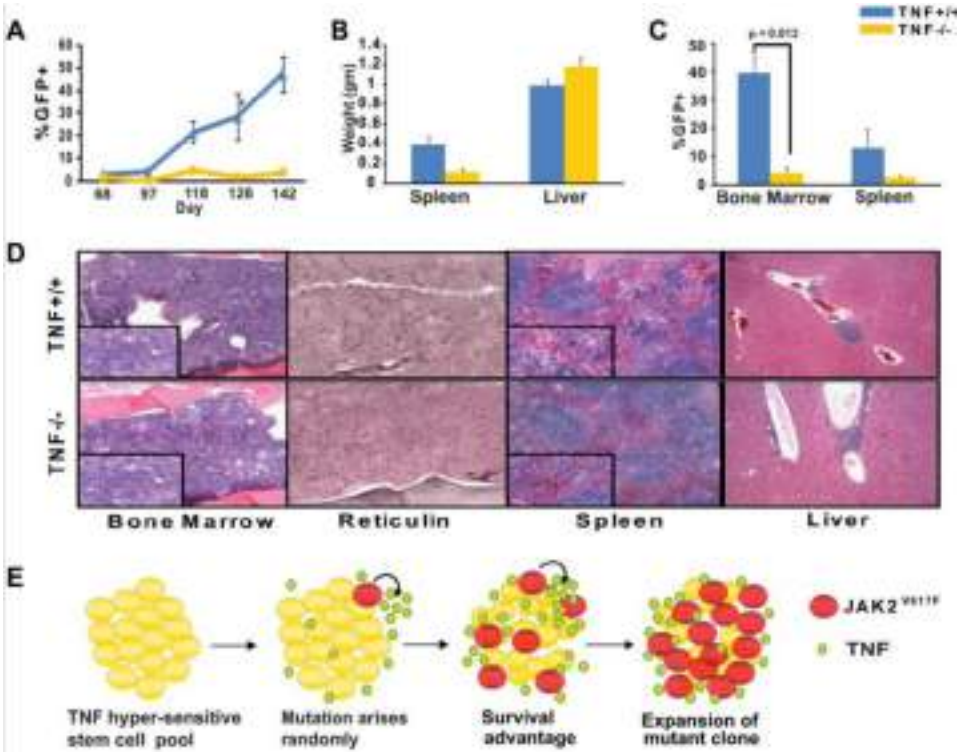


Masselli E et al Cells 2020

JAK2V617F activity is positively correlated with expression of TNFα mRNA, suggesting that **JAK2V617F directly up-regulates TNFα mRNA.**

TNFα is not required for development of MPN but promotes expansion of JAK2V617F cells in a murine transplantation model**.**

JAK2V617F induced TNF resistance provides a strong selective advantage, allowing for the expansion of the mutant clone and development of clinical disease. Maintenance of a high TNFα environment by JAK2V617F cells further enhances the selective advantage for the JAK2V617F clone.



Fleischman AG et al Blood 2011

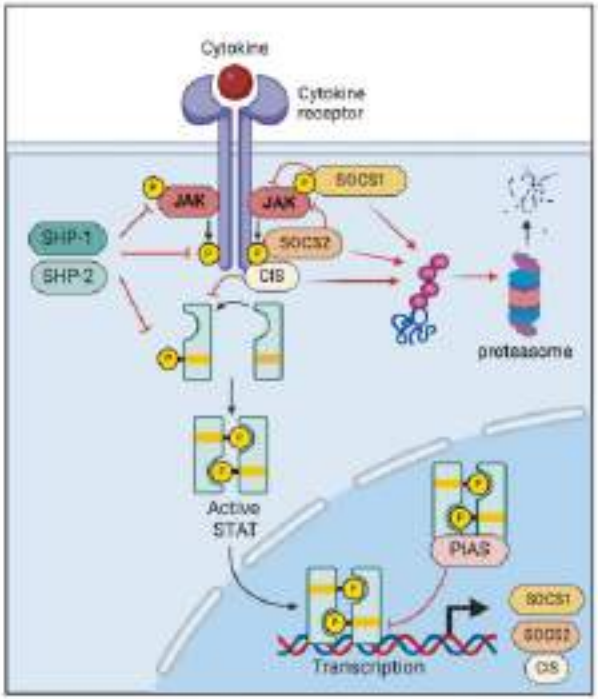


Fig. 3 Regulation of the JAK-STAT signaling cascade. CIS cytokine inducible SH2 protein, JAK Janus kinase, PIAS Protein inhibitor of activated STAT, SHP Src homology region 2 domain-containing phosphatase, SOCS suppressor of cytokine signaling, STAT Signal Transducer and Activator of Transcription.

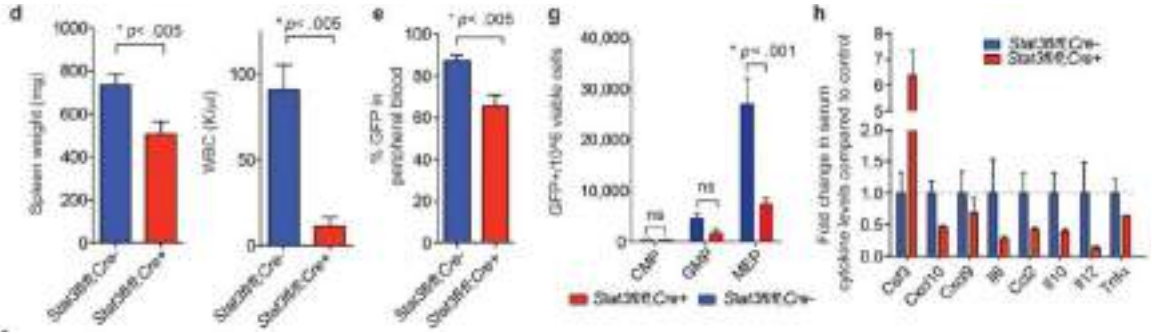
Perner F et al. Leukemia 2025

STAT-regulated expression of growth- and inflammatory factors is an evolutionarily conserved cellular response mechanism following stimulation of JAK-dependent receptors, yet a specific set of key transcriptional targets have been characterized in the presence of the JAK2-V617F mutation.

- TNFα is highly expressed by JAK2-mutated MPN cells, and its levels correlate with disease burden in primary patient cells. TNF-α is required for the development of the MPN-like disease and **JAK2WT CD34+ cells from JAK2V617F-positive patients were hypersensitive to TNF-α-induced suppression** of clonogenic growth, suggesting that MPN cells alter their immediate local environment to promote their own growth while suppressing the growth of their normal counterparts

- JAK2-V617F has been shown to be associated with increased expression of IL6 and loss-of-function polymorphisms in the IL6-receptor protection from MPN.

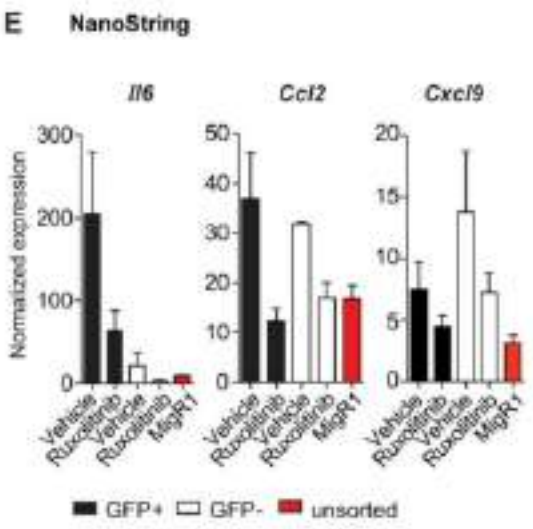
- The JAK2-V617F mutation is associated with increased expression of the chemokine CXCL10.



A set of cytokines are elevated in MPLW515L-diseased mice and ruxolitinib treatment normalized their levels.

5. Pan-hematopoietic Stat3 deletion resulted in lower white blood counts, lower spleen weights, and a reduced degree of reticulin and normalized circulating cytokine levels. In contrast, MPN-specific Stat3 deletion did not significantly attenuate cytokine production.

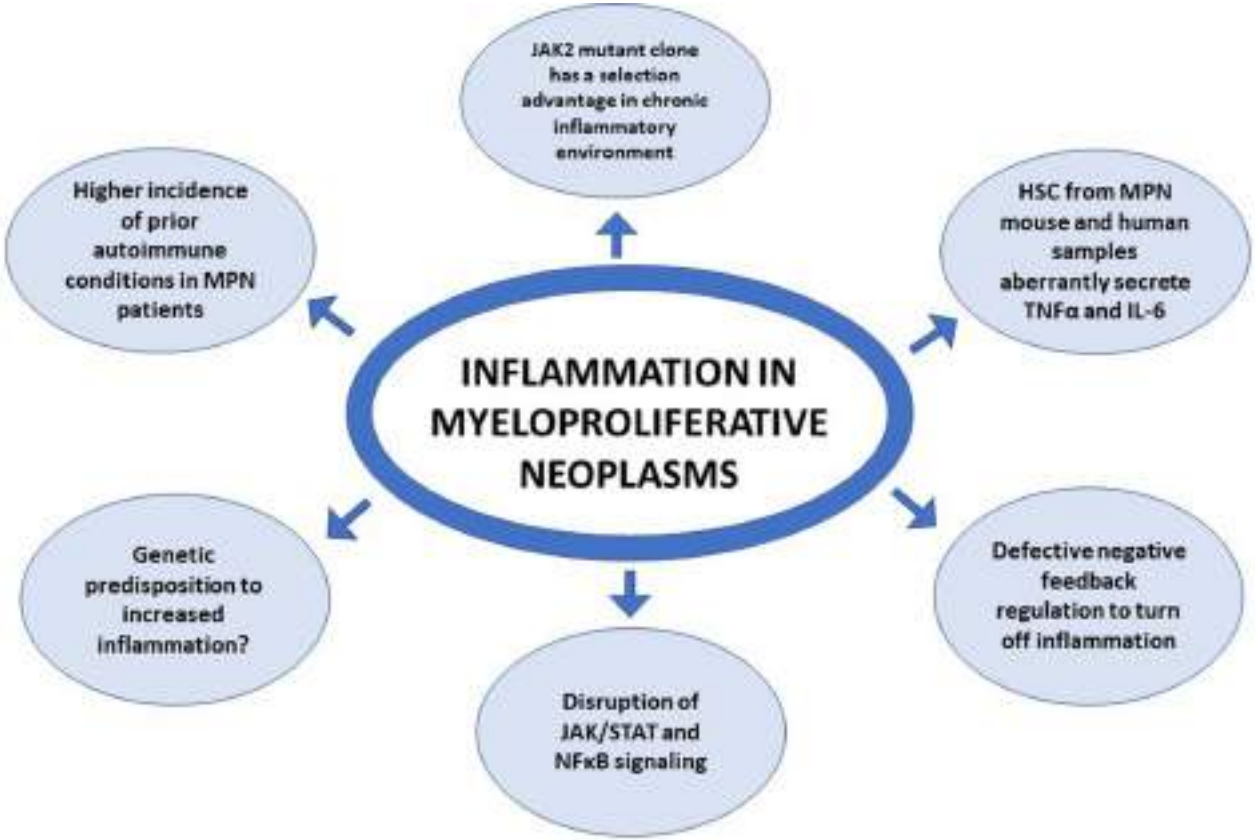
These data are consistent with a requirement for STAT3 signaling in both malignant and non-malignant hematopoietic cells in MF.



6. MPLW515L-mutant MF cells express high mRNA levels of a subset of inflammatory cytokines, including IL-6, consistent with tumor-derived cytokine production. By contrast, some cytokines, including Ccl2 and TNFα, were derived from both mutated and unmutated cells, and other cytokines, including Il12 and Cxcl9, were largely derived from non-mutant cells.

Importantly, **ruxolitinib treatment normalized cytokine expression from both cell populations** demonstrating that JAK inhibition reduces cytokine production from both tumor and non-tumor populations in vivo.

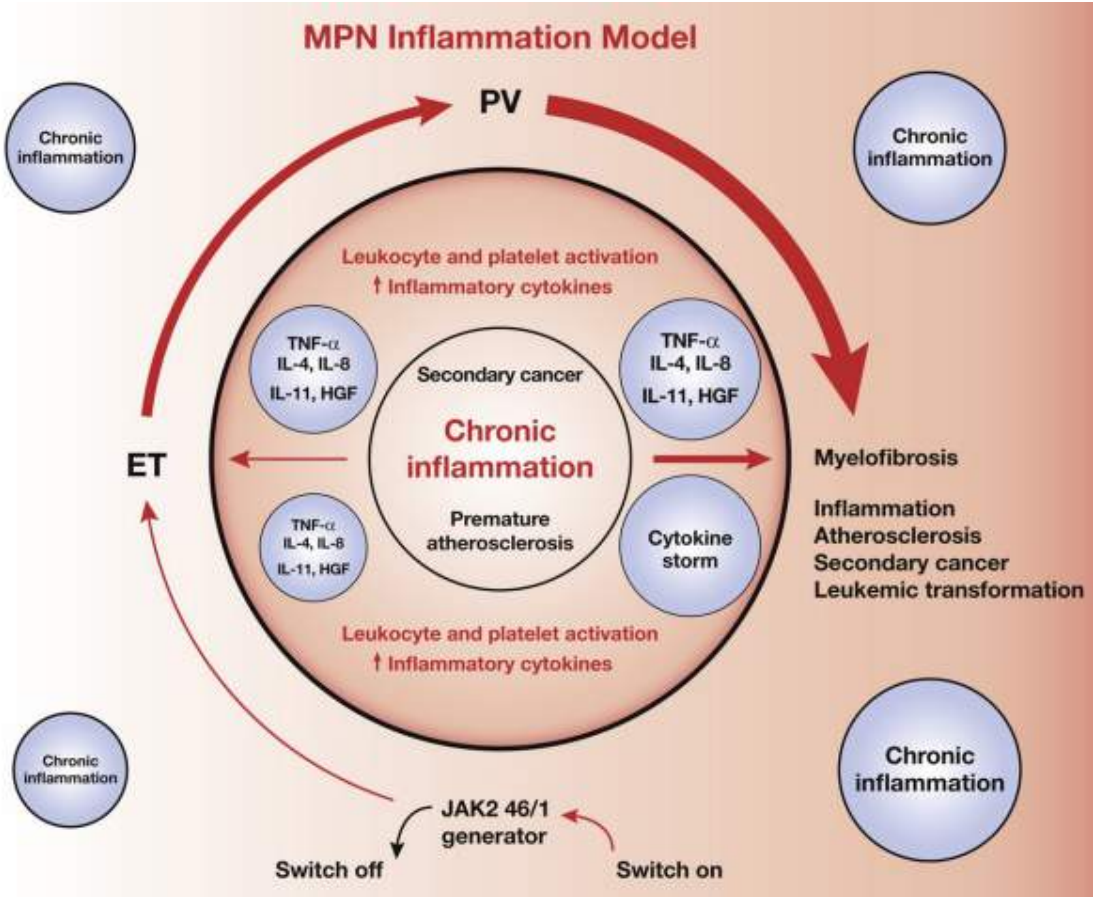
Kleppe M et al. Cancer Disc 2015



Mendez Luque LF CurrHematol Malig Rep 2019

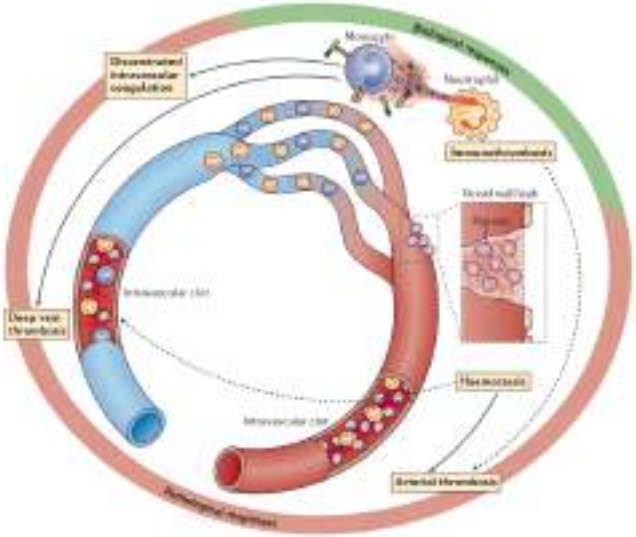
Proinflammatory cytokines have been pathologically linked to:

1. disease-associated increases in bone marrow fibrosis
2. constitutional symptoms,
3. splenomegaly,
4. extramedullary hematopoiesis,
5. leukemic evolution,
6. thrombotic risk.



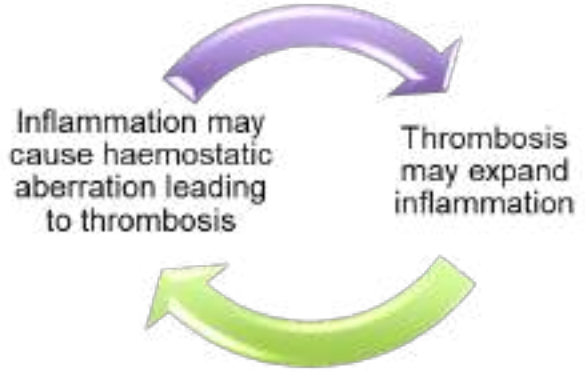
Hasselbalch HC. Cytokine Growth Factor Rev. 2013

INFLAMMATION IMPACTS ON HAEMOSTASIS



Immunothrombosis — the local formation of thrombi in microvessels supported by fibrin generation and the recruitment of immune cells and platelets — represents a mechanism of intravascular antimicrobial defence. Both haemostasis and immunothrombosis are biological processes that serve to maintain host integrity.

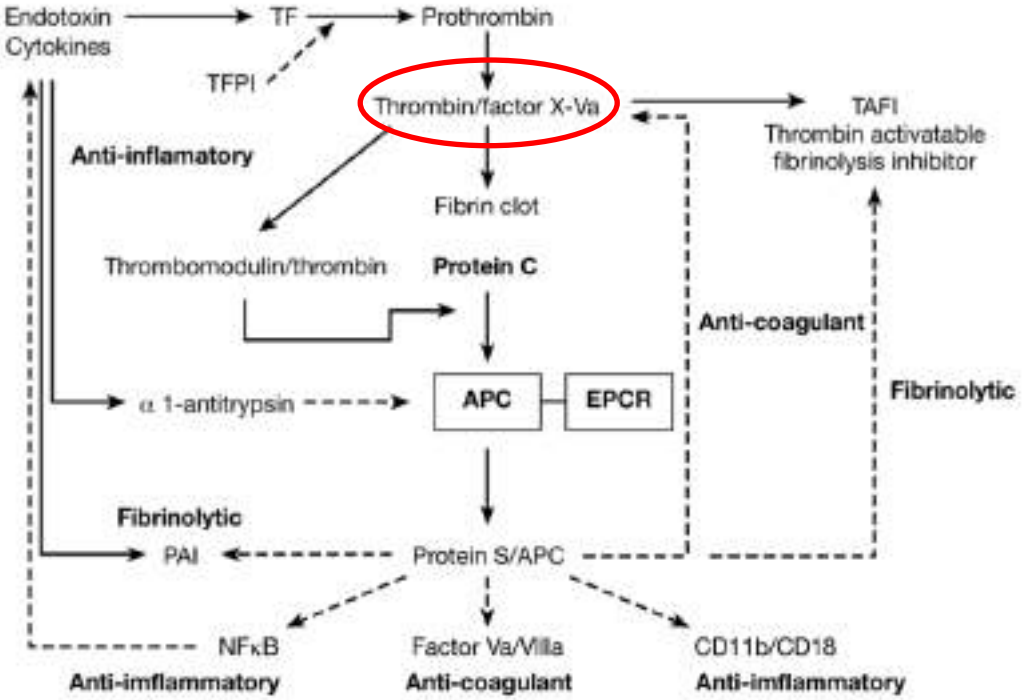
Thromboinflammation is the aberrant activation of this process and it consists in the dysregulation of the two most important defensive and wound-healing responses of the body: *inflammation and hemostasis.*



Morello S et al. Cells 2021; Engelmann B et al. Nat Rev Immunol. 2013

Impact of inflammation on coagulation:

1. Induction of tissue factor espression on leucocyte surface
2. Facilitate monocyte and endothelial interactions
3. Induce platelet activation and increase platelet production (IL-6)
4. TNF-a, IL-8 and IL-6 lead to the release of ultra-large von Willebrand factor and inhibit ADAMTS13.
5. Decrease AT and vascular heparine-like molecules
6. Downregulation of protein C pathway and thrombomodulin



Esmon C. J Thromb Haemost 2003; Webster NR. BJA 2002

Of all the coagulation factors, the inflammatory effects of **FXII, thrombin (FII), and fibrin(ogen)** have been the most well-documented.

1. FXII stimulates inflammation by interacting with the uPAR and stimulates the production of TNFα, interferon (IFN)γ, IL-1, and IL-2; FXII promotes neuthrophil degranulation and NET formation.

2. FIIa induces activation and degranulation of plateletes and the release of PAF, IL-8, RANTES, MCP-3, CCL17, CCXL1, CXCL5, and serotonin, as well as P-selectin, fibrinogen receptor GPIIb-IIIa, and CD40 ligand upregulation.

3. Fibrinogen increases the production of cytokines (TNFα, IL-1β, and IL-6), chemokines (MIP-1 and -2, MCP-1), and ROS.

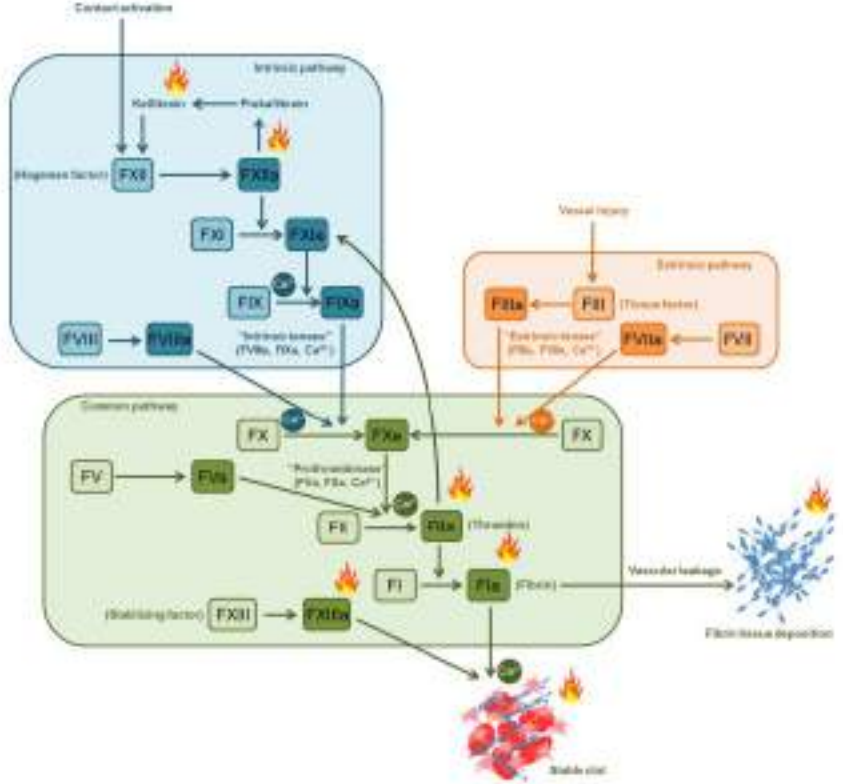


Figure 1. The mammalian blood coagulation network. The "fire" icon indicates the components of the coagulation system involved in the development of inflammation. See details in the text.

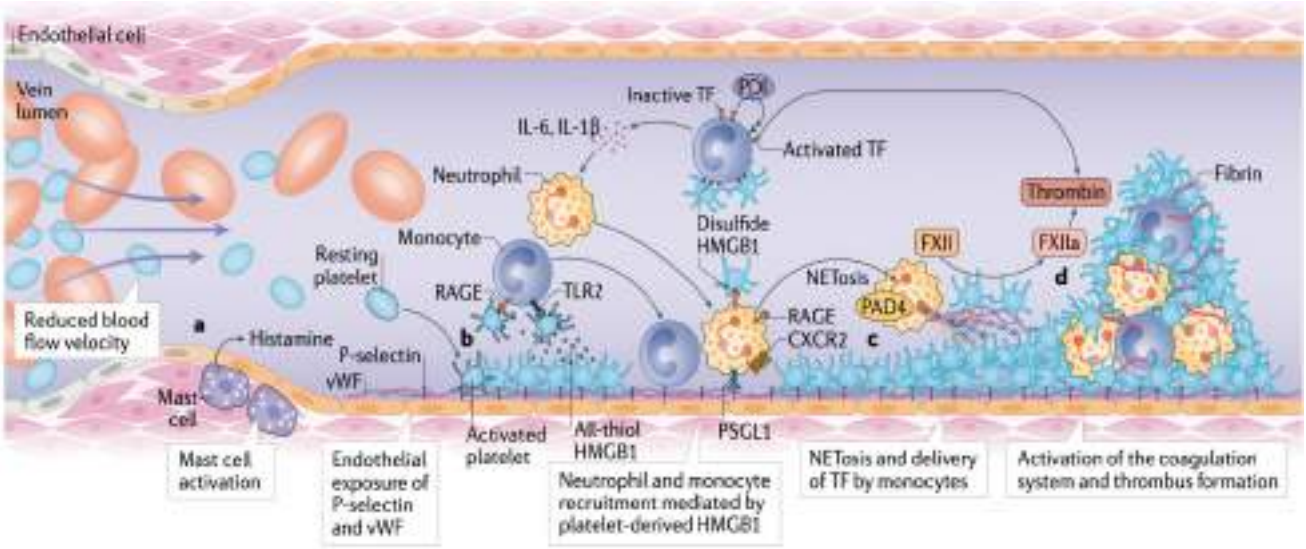
Starikova EA et al. Curr Issues Mol Biol 2025

Mutual activation of platelets and neuthrophils

1. Platelets are involved in neutrophil recruitment and activation through the release of soluble mediators, such as chemokines (including CCL5, CXCL4, CXCL5 and MIF) and serotonin, and through adhesion molecules such as via P-selectin– PSGL1 interactions.

2. The binding between platelets and neutrophils leads to a drastic change in neutrophil function. These **activated neutrophils** not only arrest at sites of thrombus formation but also **contribute to the propagation** of thrombus formation **through NETosis.**

3. **The release of cathelicidins by neutrophils during thrombosis induce platelet degranulation and the release of pro-inflammatory mediators,** such as HMGB1 and IL-1β, without inducing platelet aggregation. Cathelicidin-primed platelets interact with neutrophils through P-selectin, which fosters neutrophil activation and NETosis.



Stark K & Massberg S. Nat Rev Cardiol. 2021

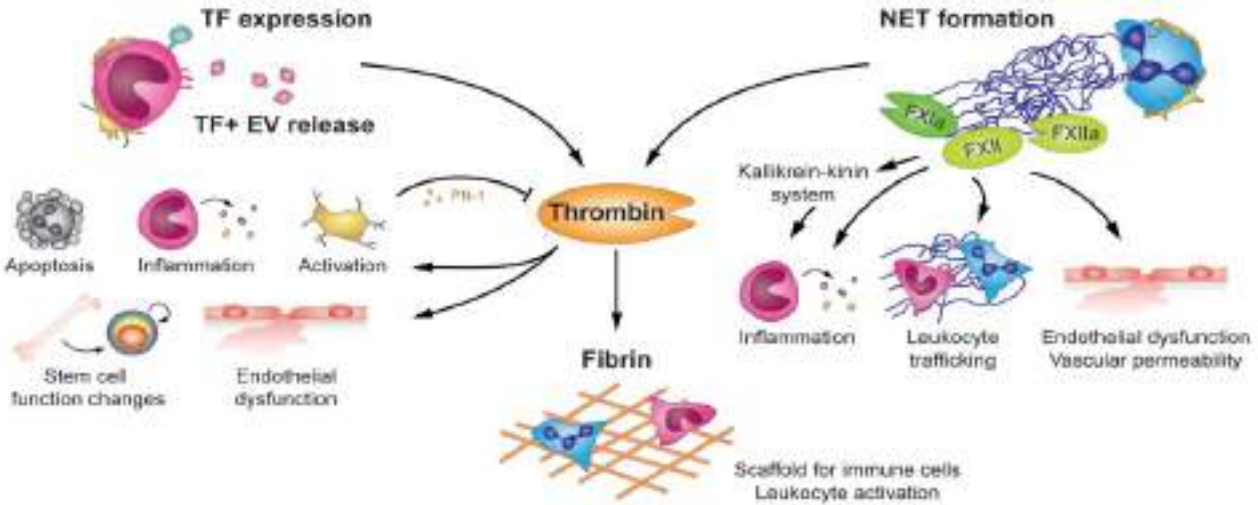
Tissue factor: upon inflammation monocytes, extracellular vescicles and platelet express TF

Contact pathway: extracellular traps can activate the contact pathway

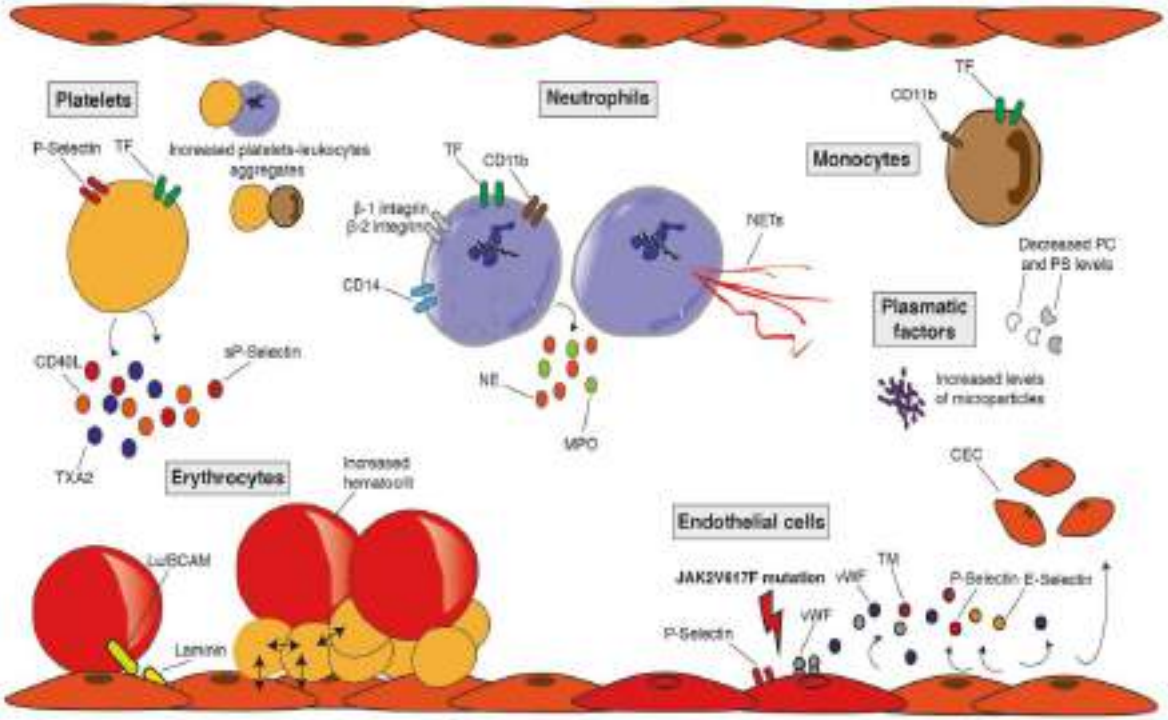
G protein-coupled protease-activated receptors (PARs): proteases can activate PAR1 and PAR 2 inducing platelet activation, a proinflammatory phenotype in leukocytes and modulate stem cells function.

Neuthrophils extracellular traps (NETs): provide negative charged surface that captures coagulation factors and platelet. Neutrophil elastase on NETs inactivates anticoagulant mechanisms via cleavage of thrombomodulin and TFPI.

FXII: augments leukocyte mobility and contributes to endothelial dysfunction, leading to enhanced vascular permeability



Schrottmaier WC & Assinger A. Hamostaseologie 2024



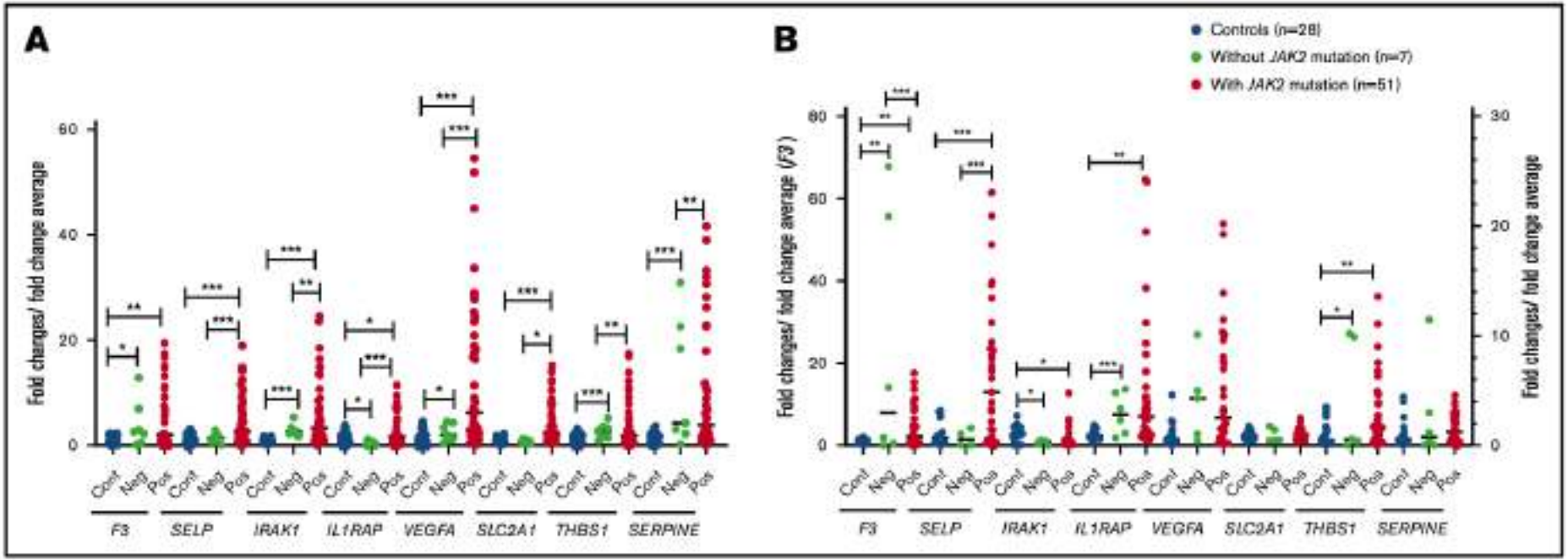
Many studies have demonstrated an increased coagulation activation in MPNs subjects compared healthy subjects.

In MPNs patients there are:

- Increased levels of Ddimer, FV, FVIII, vWF, TF and thrombin generation
- Decreased levels of protein C and S
- Resistance to activated protein C and thrombomodulin
- Decreased concentration of PAI-1 and TPA

Guy A et al. Leukemia 2021

Thrombo-inflammatory genes are upregulated in MPN granulocytes and plateletes and correlate with thrombosis history.

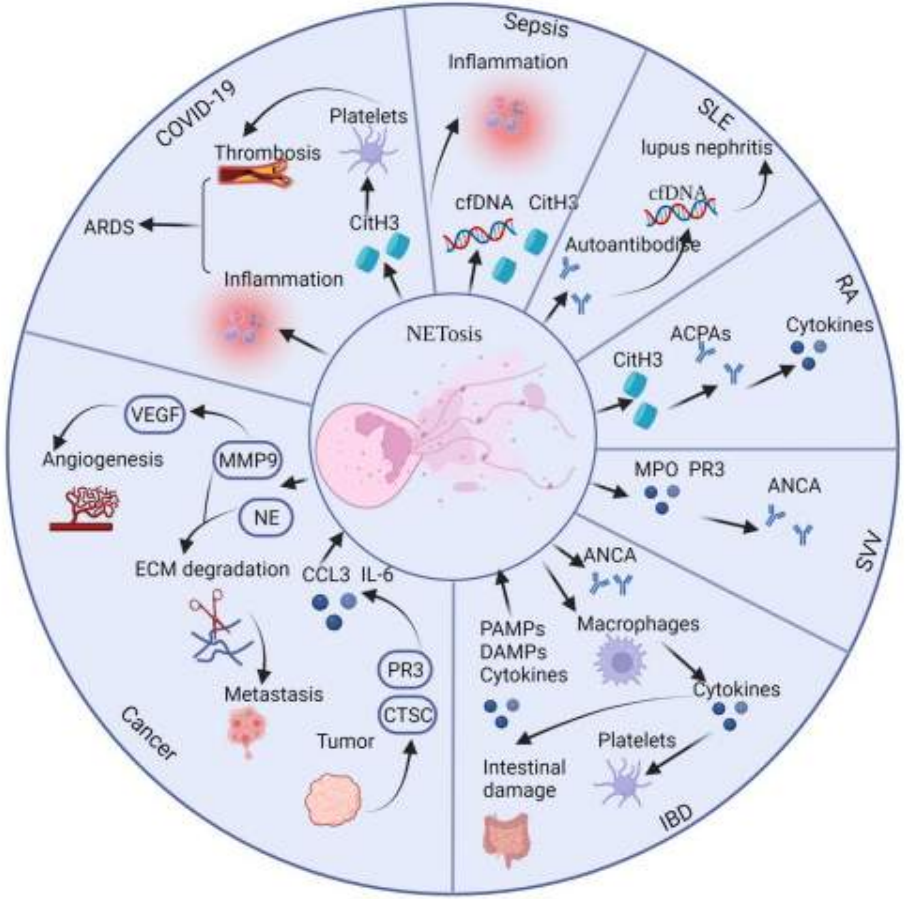


Gengaraju R et al. Blood 2020

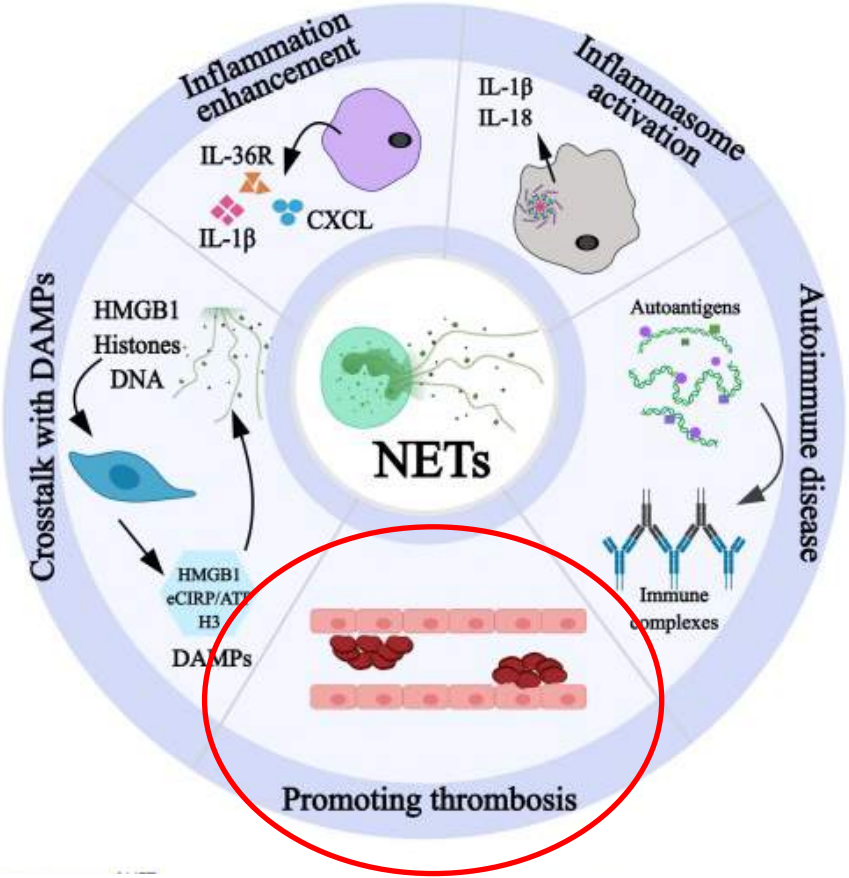
ROLE OF NETs IN MPN THROMBOSIS

On stimulation, normal neutrophils can expel extracellular strands of decondensed DNA in complex with histones and other neutrophil granular proteins to produce neutrophil extracellular traps (NETs). These structures have the ability to ensnare microorganisms and have also been implicated in the pathogenesis of autoimmunity and thrombosis.

NETs are always accompanied by inflammation as a part of the immune response. Many stimuli that cause inflammation induce NETosis, whereas NETs promote the onset and worsening of inflammation, as seen in sepsis, diabetes, and rheumatoid arthritis (RA)



Huang J, Hong W, Wan M, Zheng L.. MedComm (2020). 2022



NETs mediate platelet activation, coagulation, and thrombosis.

In the plasma-induced NETs model of COVID-19, SARS-CoV-2 activates complement C3 to drive platelet/NETs and induce the formation of NETs enriched with tissue factor, which in turn activates endothelial cells to express tissue factor, thus increasing their procoagulant activity, and further activates platelets to aggravate the inflammatory cycle.

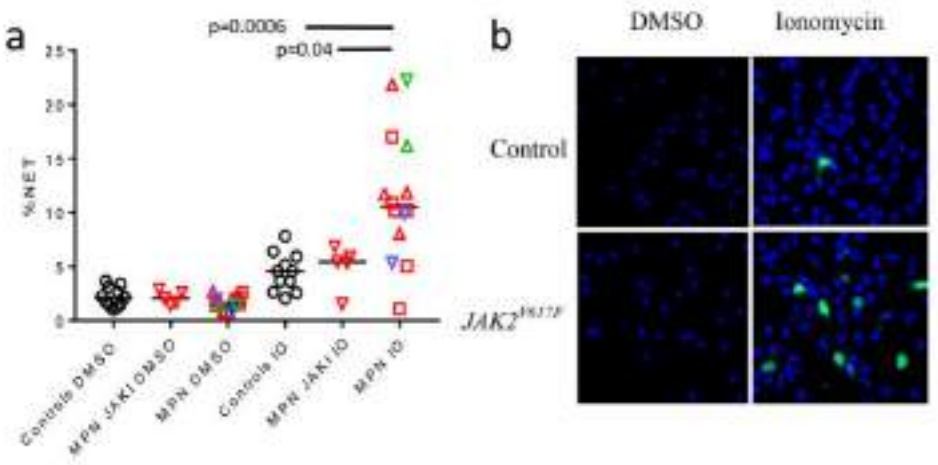
Platelet factor 4 coagulation factor signaling in platelets binds to NETs, making them robust and resistant to DNase and leads to microthrombosis in patients with COVID-19.

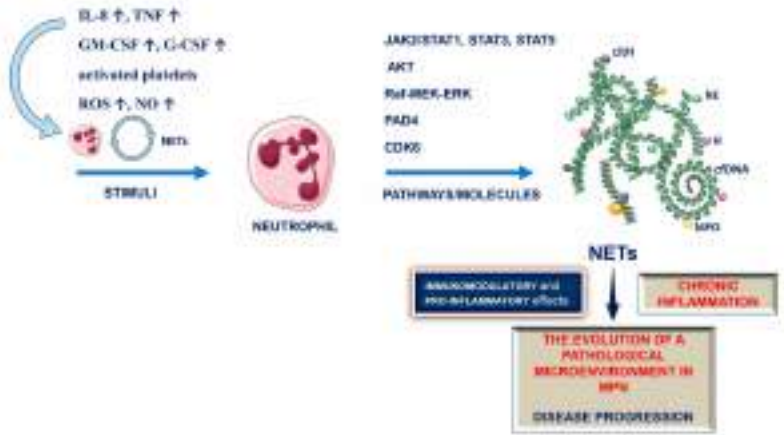
Li X, et al. . Int J Nanomedicine. 2023

Neutrophils derived from patients with MPNs are associated with an increase in NET formation that is blunted by ruxolitinib.

Jak2V617F-driven MPN mouse models have a NET-rich, prothrombotic phenotype

PAD4 is overexpressed in MPNs and is essential for the NET-driven prothrombotic phenotype in Jak2V617F-driven MPN mouse models

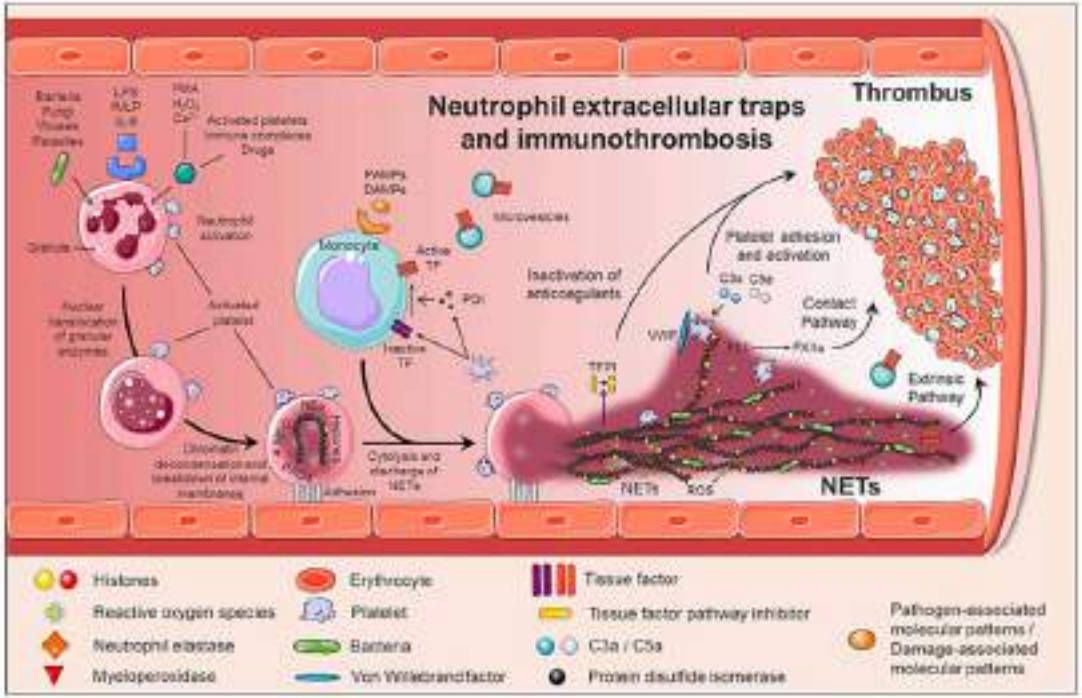




Various stimuli that could activate NET formation are present in MPNs: the elevation of cytokines and chemokines, activated platelets, elevated ROS and NO.

Most importantly, members of the STAT family of transcription factors (STAT1, STAT3 and STAT5) were recently reported as important for NET formation.

Wolach O, et al. Sci Transl Med. 2018; Marković DC et al. Int J Mol Sci. 2023



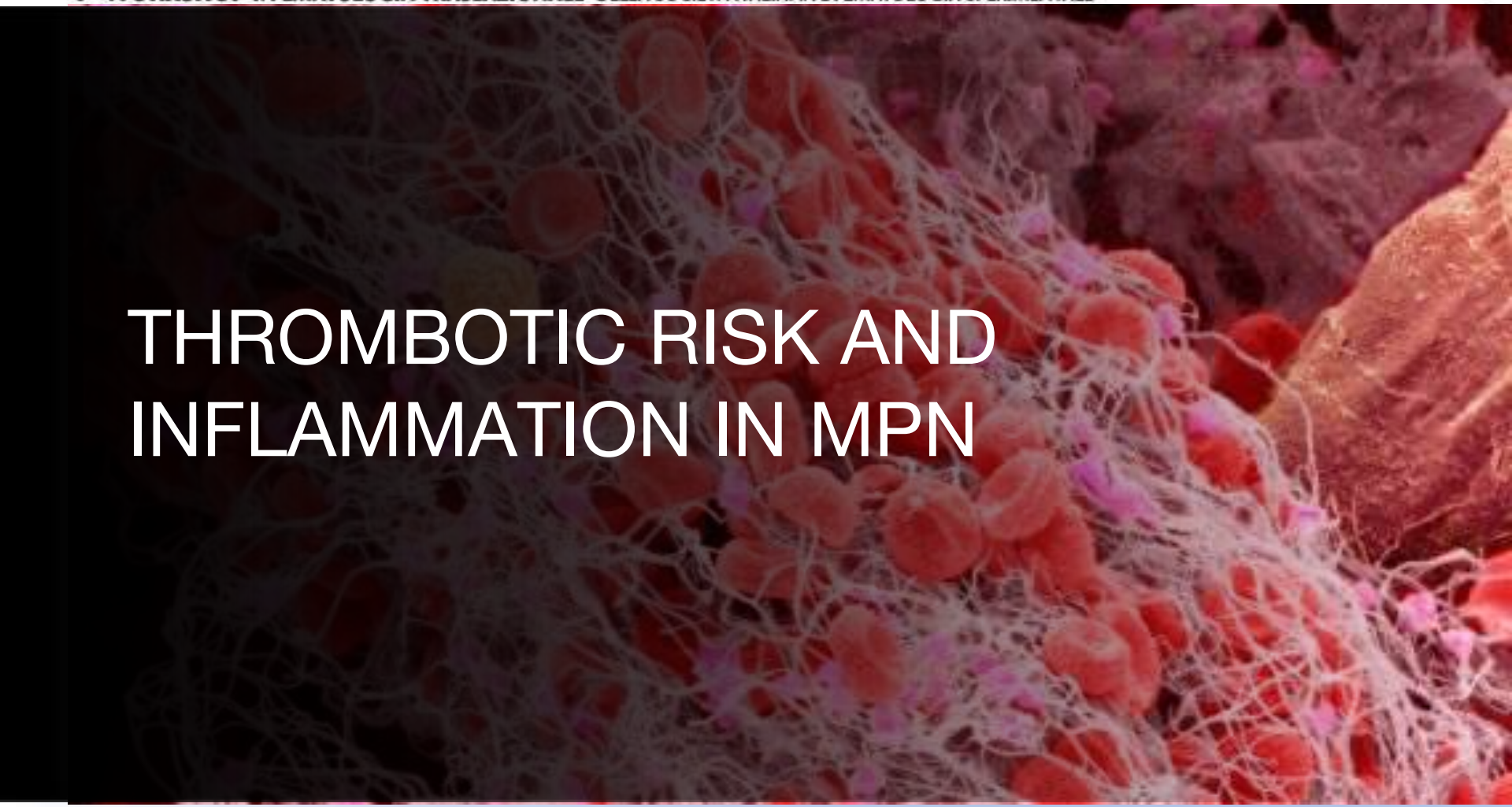
1. The presence of **DNA negative charges causes an activation of FXII**, a plasma serine protease, initiating the intrinsic pathway of coagulation.

2. **Histones** are the most abundant proteins in NETs and **are able to activate platelets,** favoring their aggregation and contributing to the generation of thrombin.

3. **Elastase and Cathepsin G** are enzymes derived from neutrophils and the most abundant proteins in NET after histones. Elastase **causes the degradation and inactivation of TFPI and AT.**

4. **TF has been identified in NETs** and it has been documented that this factor comes not only from monocytes that migrate to the inflamed area, but also from neutrophils.

Ferrer-Marín F et al.. Int J Mol Sci. 2021



THROMBOTIC RISK AND INFLAMMATION IN MPN

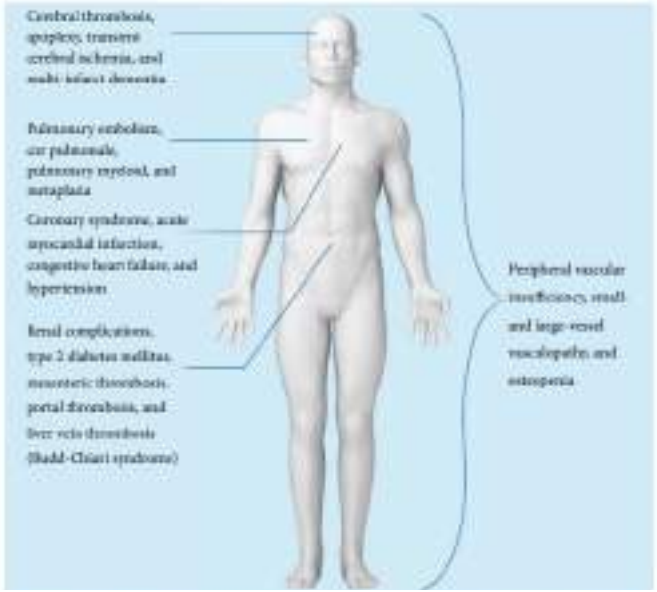


Table 2. Pooled Prevalence of Venous, Arterial Thrombosis and of Bleeding Complications Per Localization.

Venous thrombosis	Arterial Thrombosis	Hemorrhage
• Pooled prevalence : 6.2%	• Pooled prevalence: 16.2%	• Pooled prevalence : 6.2%
• Deep vein thrombosis : 3.4%	• Cerebrovascular disease : 7.4%	• Mucocutaneous bleeding : 2.8%
• Splachnic vein thrombosis : 1.4%	• Transient Ischemic Stroke : 3.5%	• Gastrointestinal bleeding :2.1%
• Pulmonary embolism : 0.9%	• Coronary artery disease : 6.1%	• Epistaxis: 1%
• Cerebral sinus thrombosis : 0.7%	• Peripheral artery disease: 3.3%	• Postoperative bleeding: 1.1%

Hasselbalch HC. Mediators Inflamm 2018; Papageorgiou L et al. Clinical and Applied Thrombosis/Hemostasis. 2022.

TABLE 1 Impact of Driver Mutation and Clonal Hematopoiesis of Indeterminate Potential–Associated Mutations on Thrombosis in Patients With Myeloproliferative Neoplasms

First Author, Ref. #	MPNs Studied	N	Cardiovascular Outcomes	Effect of *JAK2* Mutation on Thrombosis	Effect of CHIP Mutation on Thrombosis	Comments
Carobbio et al[21]	ET	891	Arterial thrombosis	HR: 2.57 (95% CI: 1.27-5.19) vs no *JAK2* mutation	NA	
Tefferi et al[32]	ET and PV	316	Any thrombosis	For ET: RR: 4.8 (95% CI: 1.6-14.2) *JAK2* vs *CALR*	For ET: *TET2* mutation associated with increased risk for thrombosis (RR: 3.4; 95% CI: 1.4-8.4)	No association between adverse mutations (including *TET2*, *ASXL1*) with thrombosis in patients with PV
Guglielmelli et al[23]	PV	576	Arterial and venous thrombosis	$JAK2^{V617F}$ VAF >50% Arterial thrombosis: HR: 0.9 (95% CI: 0.5-1.6) Venous: HR: 3.8 (95% CI: 1.7-8.6)	NA	
Segura-Diaz et al[31]	PV	16	Any thrombosis	NA	≥1 mutation in *TET2*, *DNMT3A*, or *ASXL1* was associated with increased risk for thrombosis (OR: 4.68; 95% CI: 1.49-14.64)	
Cerquozzi et al[20]	PV	587	Arterial thrombosis	NA	No difference between *TET2* (14% with arterial thrombosis vs 20% without; $P = 0.40$) or *ASXL1* (12% vs 10%; $P = 0.80$)	
Rumi et al[22]	PMF	617	Any thrombosis	SHR: 2.19 (95% CI: 1.15-4.18) vs *CALR* mutation	NA	No difference in leukemia-free survival between *JAK2* and *CALR* mutations Worse overall survival with *JAK2* compared with *CALR* (HR: 2.3; $P < 0.001$)
Barbui et al[41]	PMF	707	Any thrombosis	HR: 1.92 (95% CI: 1.10-3.34) vs no *JAK2* mutation	NA	

ASXL1 – additional sex Combs-like 1;*CALR* – calreticulin; CHIP – clonal hematopoiesis of indeterminate potential; *DNMT3α* – DNA methyltransferase 3 alpha; ET – essential thrombocythemia; *JAK2* – Janus kinase 2; MPN – myeloproliferative neoplasm; NA – not applicable; PMF – primary myelofibrosis; PV – polycythemia vera; RR – relative risk; SHR – subdistribution HR; *TET2* – tet methylcytosine dioxygenase 2; VAF – variant allele fraction.

Leiva O et al. JACC CardioOncol 2022

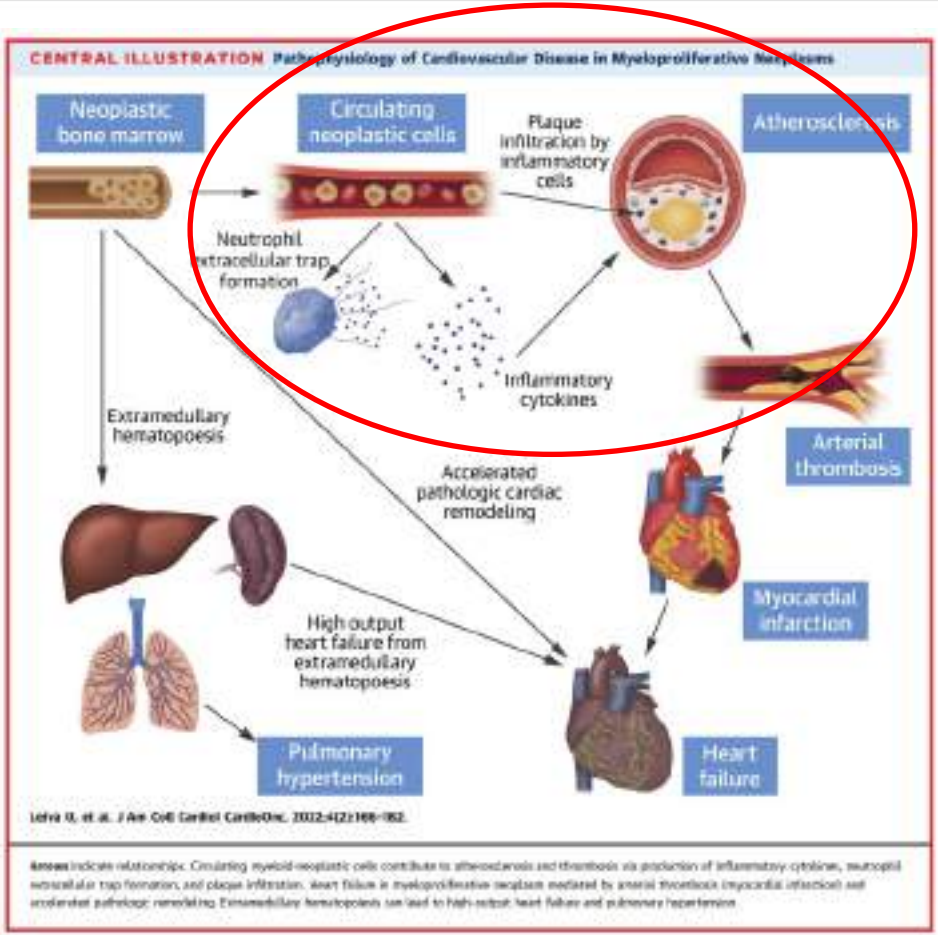
MPN patients are at increased risk of CVD including heart failure (HF), atrial fbrillation (AF), and pulmonary hypertension (PH). Additionally, cardiovascular risk factors, including hypertension, smoking, chronic kidney disease, and diabetes are common among patients with MPN.

Furthermore:

- Increased heart failure risk in patients with MPNs may involve accelerated adverse cardiac remodeling and inflammation.

- Pulmonary hypertension can occur in patients with MPNs, especially those with primary myelofibrosis, and likely has a multifactorial etiology.

- Patients with **JAK2V617F-induced MPNs have accelerated atherosclerosis** contributed by inflammation and/or defective macrophage lipid efflux and efferocytosis.



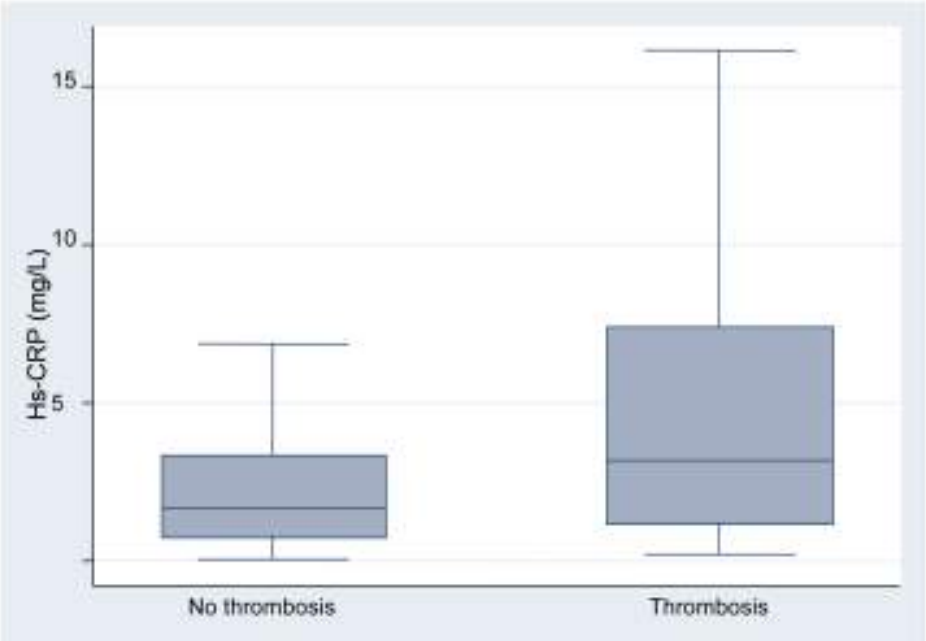
Leiva O et al. JACC CardioOncol 2022

High sensitivity C-reactive protein and pentraxin 3 were measured in 244 consecutive essential thrombocythemia and polycythemia vera patients in whom, after a median follow up of 5.3 years (range 0-24), 68 cardiovascular events were diagnosed.

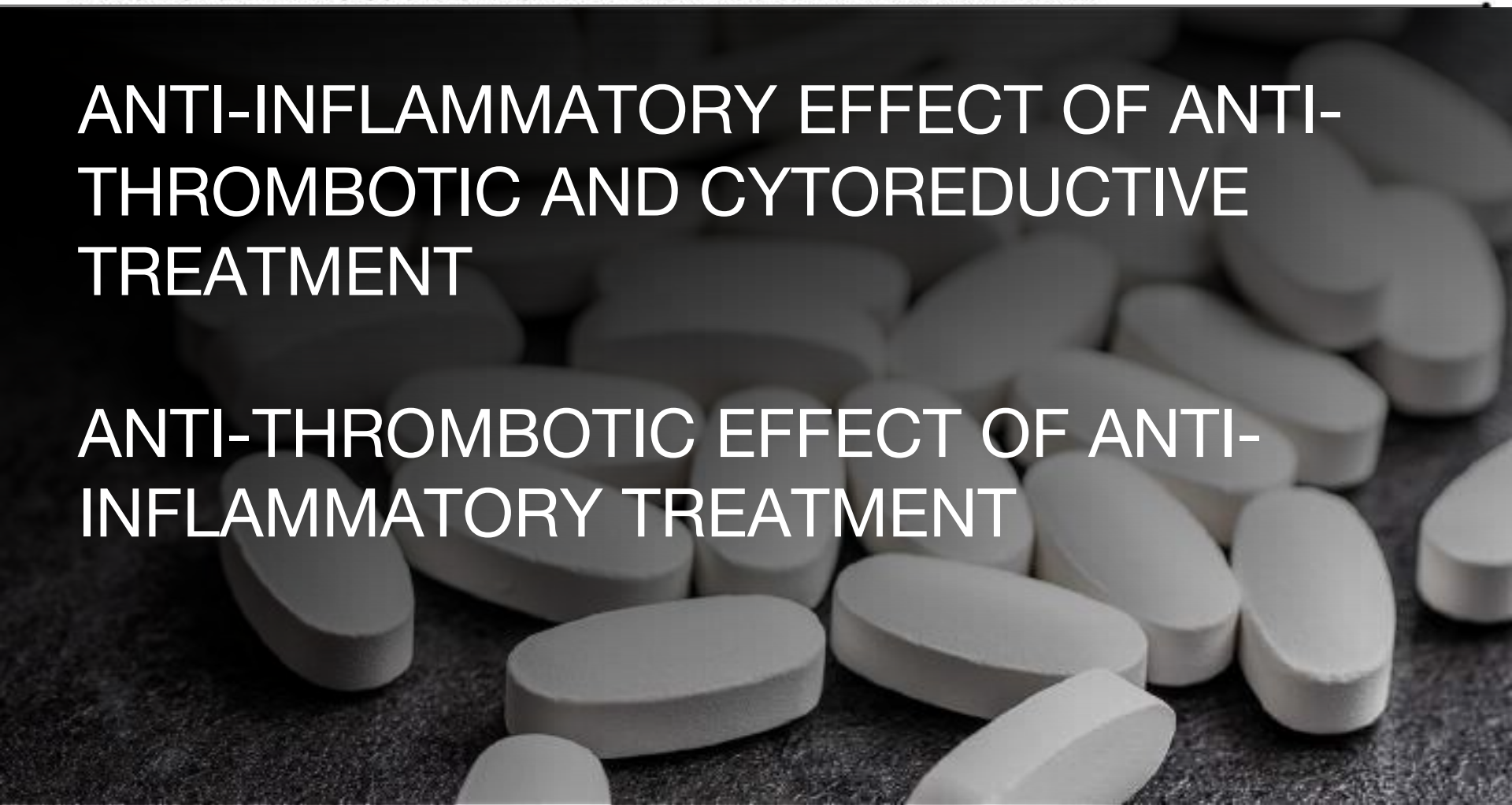
The highest C-reactive protein tertile was compared with the lowest (>3 vs. <1 mg/L) and correlated with age (P=0.001), phenotype (polycythemia vera vs. essential thrombocythemia, P=0.006), cardiovascular risk factors (P=0.012) and JAK2V617F allele burden greater than 50% (P=0.003).

Major thrombosis rate was higher in the highest C-reactive protein tertile (P=0.01) and lower at the highest pentraxin 3 levels (P=0.045).

These associations remained significant in multivariate analyses and indicate that blood levels of high sensitivity C-reactive protein and pentraxin 3 independently and in opposite ways modulate the intrinsic risk of cardiovascular events in patients with MPNs.



Barbui T et al. Haematologica 2011



ANTI-INFLAMMATORY EFFECT OF ANTI-THROMBOTIC AND CYTOREDUCTIVE TREATMENT

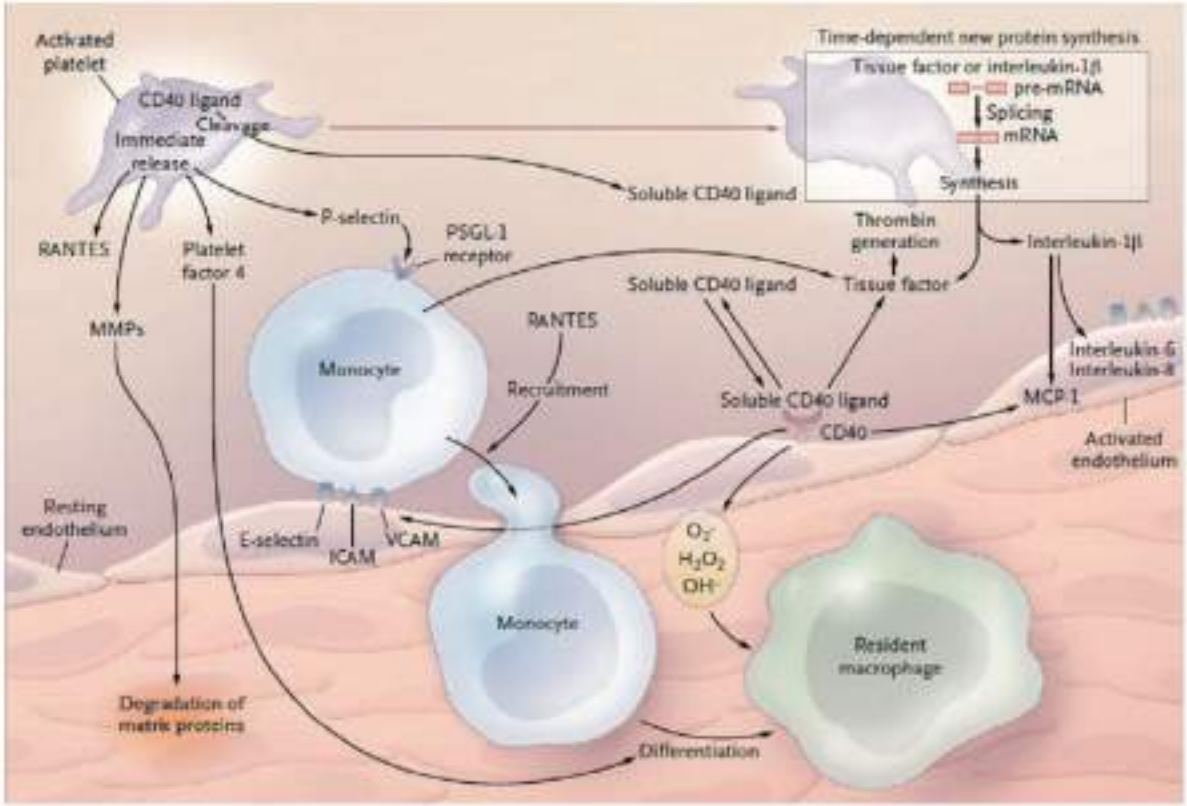
ANTI-THROMBOTIC EFFECT OF ANTI-INFLAMMATORY TREATMENT

Table 1 | **Anti-inflammatory effects of antithrombotic medications**

Medication	Antithrombotic effects	Anti-inflammatory effects	Refs
Heparin	Inhibition of coagulation	Disruption of neutrophil extracellular traps	21,22
		Neutralization of histones	210
Low-dose aspirin	Inhibition of platelet activation	Increased synthesis of the pro-resolution mediator 15-epi-lipoxin A4	214,215
$P2Y_{12}$ receptor inhibitors	Inhibition of platelet activation	Decreased pro-inflammatory mediator release	228,229
Direct-acting oral anticoagulants	Inhibition of coagulation	Inhibition of protease-activated receptors, which induce the expression of chemokines, cytokines and adhesion molecules	206–209

Stark K & Massberg S. Nat Rev Cardiol. 2021

FIGURE 3 Platelet-Derived Mediators of the Inflammatory Response

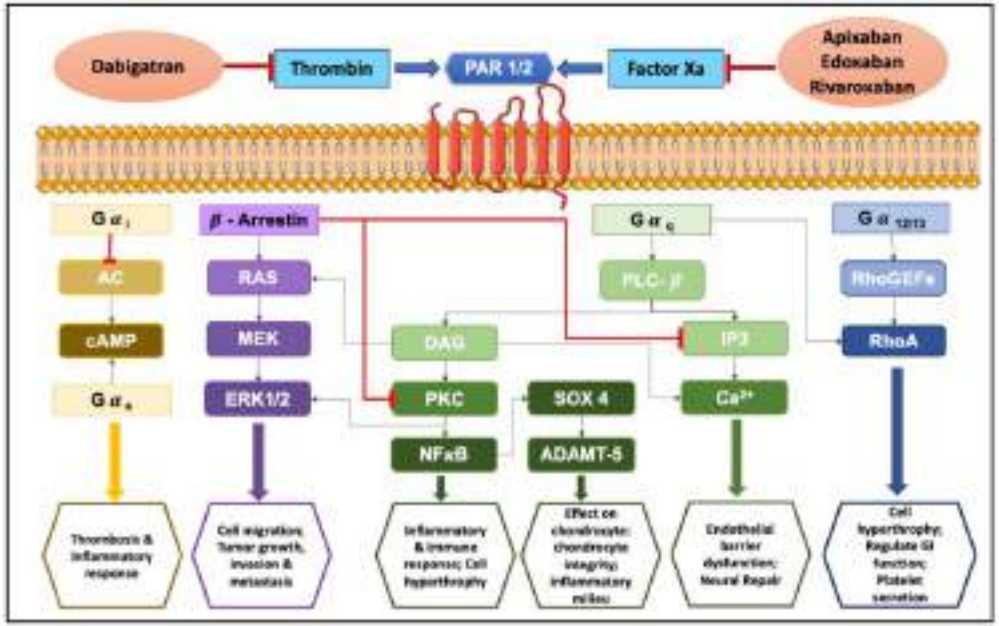


Patrono C. JACC 2015

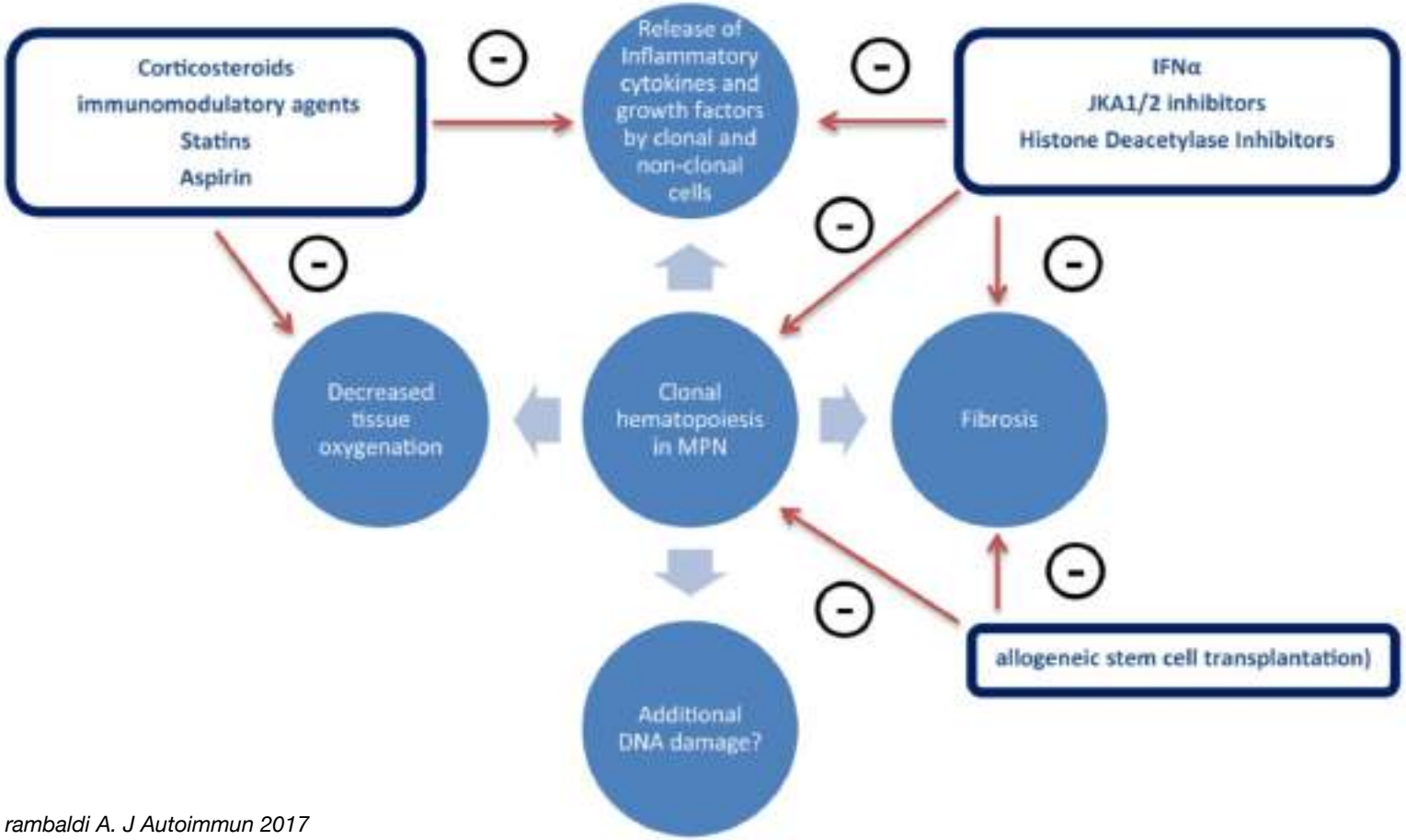
Inactivation of platelet cyclooxygenase (COX)-1 by low-dose aspirin leads to long-lasting suppression of thromboxane (TX) A2 production and TXA2-mediated platelet activation and aggregation.

Activated platelets release inflammatory and mitogenic substances into the microenvironment, primarily altering the chemotactic, adhesive, and proteolytic properties of the endothelium.

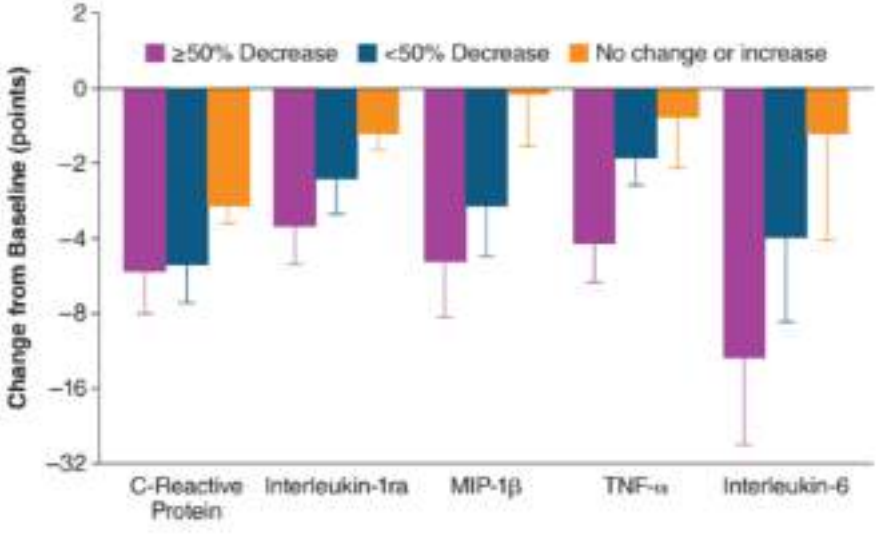
NOACs have shown to have an anti-inflammatory role through the indirect inhibition of PARs. Beyond their critical roles in blood coagulation, FXa and thrombin orchestrate a myriad of physiological processes, predominantly mediated through a family of G-protein coupled receptors protease-activated receptors (PARs). These include influencing inflammation, cell proliferation, and tissue repair mechanisms. By synthesizing current research, it posits that NOACs, traditionally used for their anticoagulant properties, may also modulate inflammation through PAR-signaling pathways, suggesting a broader clinical utility in managing inflammatory conditions and atherosclerosis.



Jannati S et al. Int J Mol Sci 2024

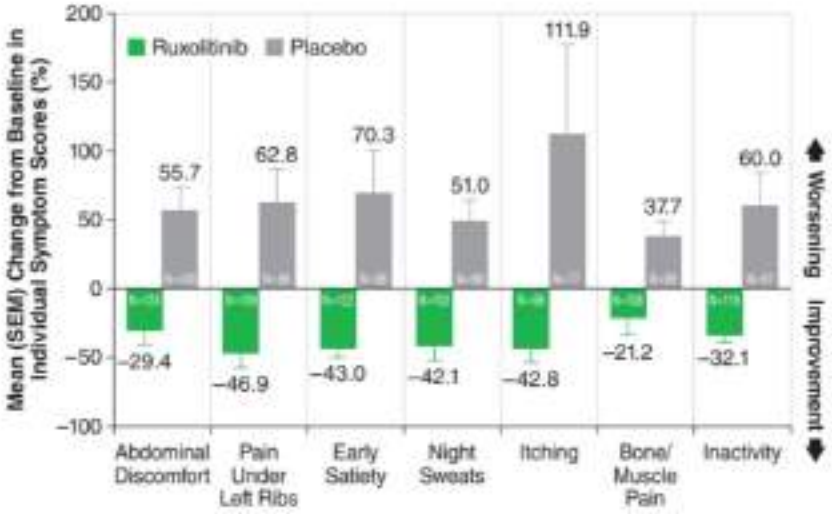


Lussana F & rambaldi A. J Autoimmun 2017



In phase I/II Ruxolitinib showed an improvement in clinical data and symptoms. Furthermore correlative marker results suggest that **the mechanism of action of ruxolitinib was at least partially based on decreases in the levels of proinflammatory cytokines,** as improvements of clinical symptoms were associated with decreases in the plasma levels of IL-1RA, MIP-1 (macrophage inflammatory protein-1), TNF-, and IL-6, which were all elevated at baseline but decreased following ruxolitinib treatment

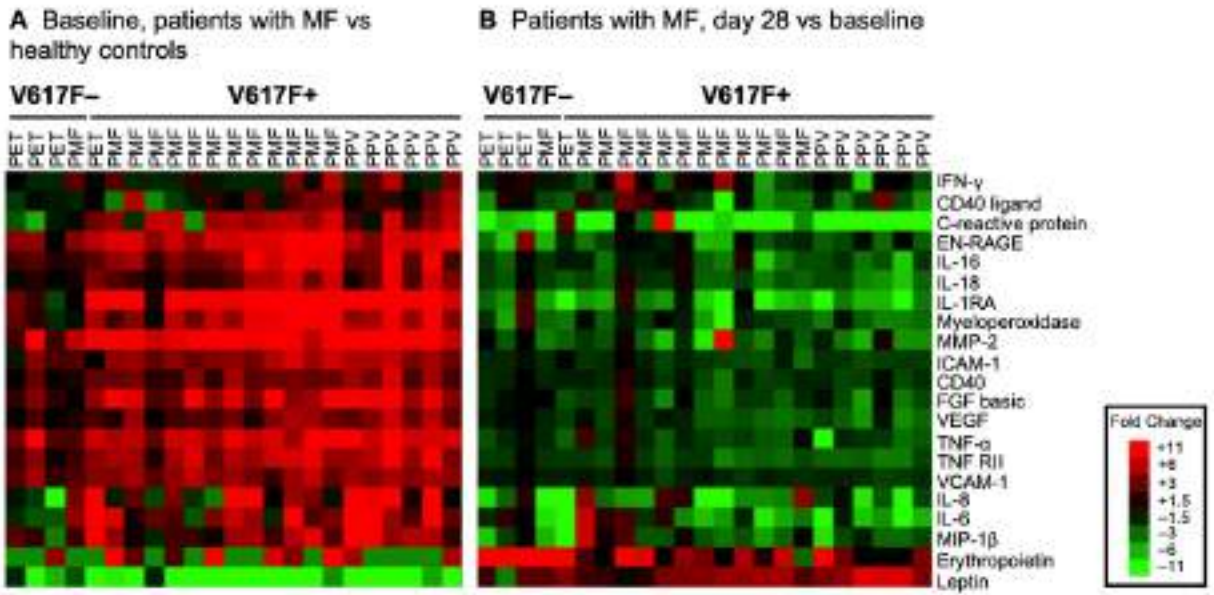
Mascarenhas J et al. Curr Med Chem 2012



In COMFORT-1 study at 24 weeks, 45.9% of ruxolitinib-treated patients showed a 50% reduction in Total Symptom Score from baseline compared to 5.3% in the placebo group (P <0.001). **There was a mean 46.1% improvement in TSS in ruxolitinib-treated patients** compared with a mean 41.8% worsening in the placebo group (P <0.001). The majority of responders had achieved a response within the first 4 weeks.

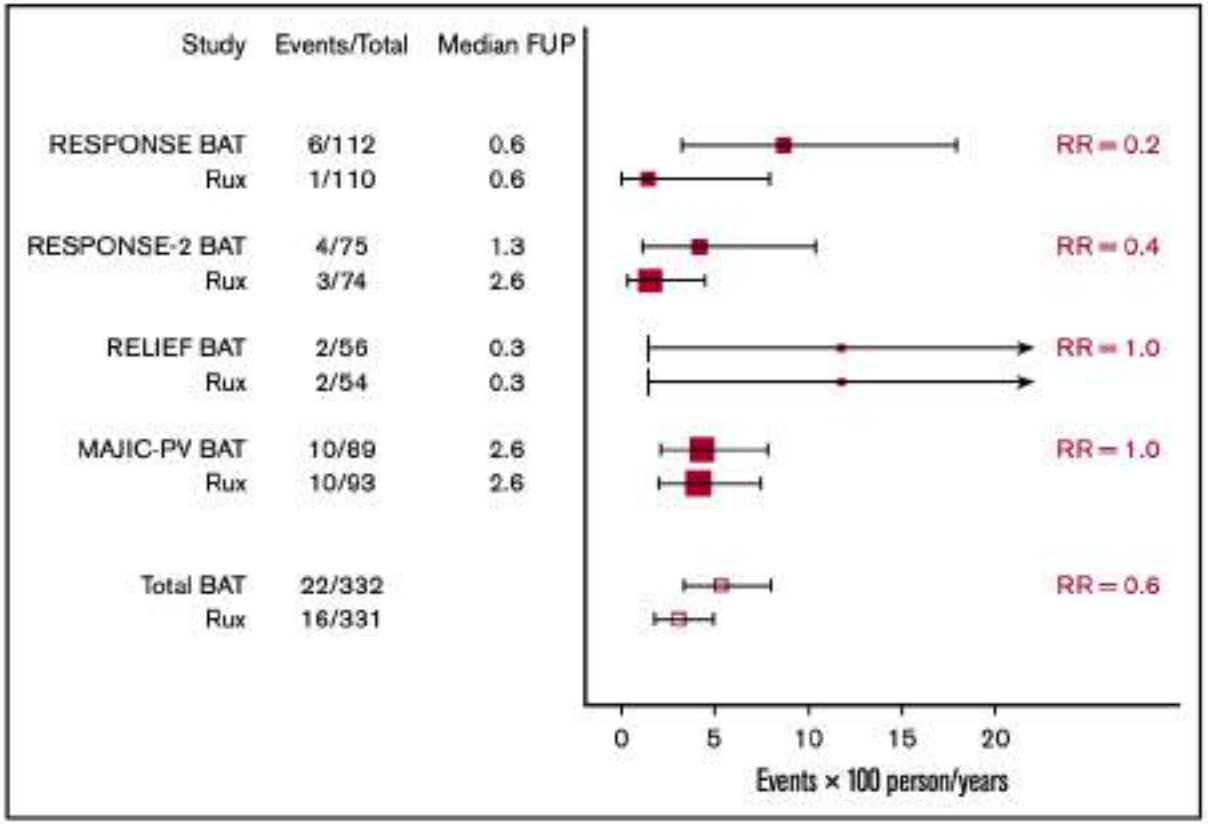
Plasma levels of pro-inflammatory cytokines, including IFN-α, IL-6, IL-8, IL-16, IL-18, as well as C-reactive protein, intracellular adhesion molecule 1, vascular adhesion molecule 1, and matrix metalloproteinase 2, were significantly higher at baseline in patients with MF compared with healthy controls (Fig. 3A**). After one cycle of therapy with ruxolitinib (28 days), levels of these pro-inflammatory biomarkers decreased (Fig. 3B).**

These changes were not related to JAK2 mutational status or disease subtype, indicating that the effects of ruxolitinib in patients with MF are reflective of a broad anti-inflammatory effect.



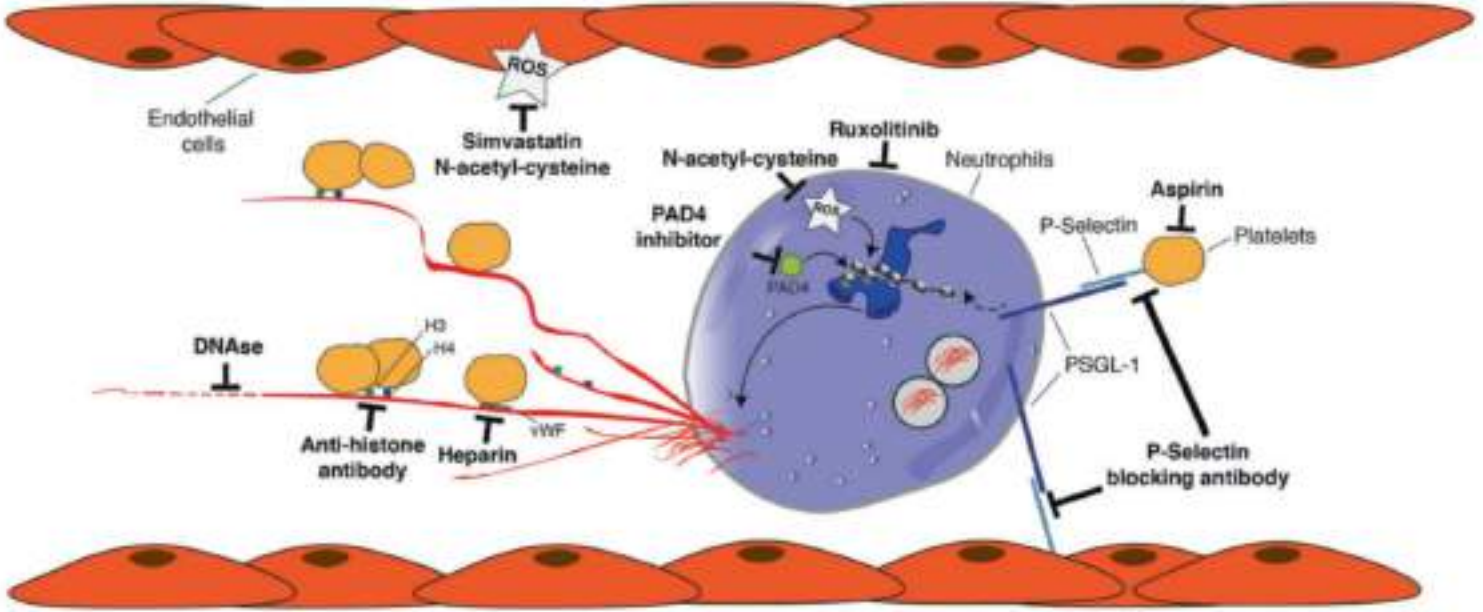
Green denotes markers that decreased with ruxolitinib treatment, and red denotes markers that increased with therapy.

Harrison C et al. JCO 2023



The thrombosis annual incidence rate is 3.09 patients per year (95% CI, 1.22-4.96) for ruxolitinib, 5.51 (95% CI, 3.72- 7.30) for BAT, and 4.30 (95% CI, 3.00-5.60) globally, with an RR for ruxolitinib vs BAT of 0.56. **The evidence of an advantage of ruxolitinib is suspect (P=0.098) but not always significant.**

Masciulli A et al. Blood 2020

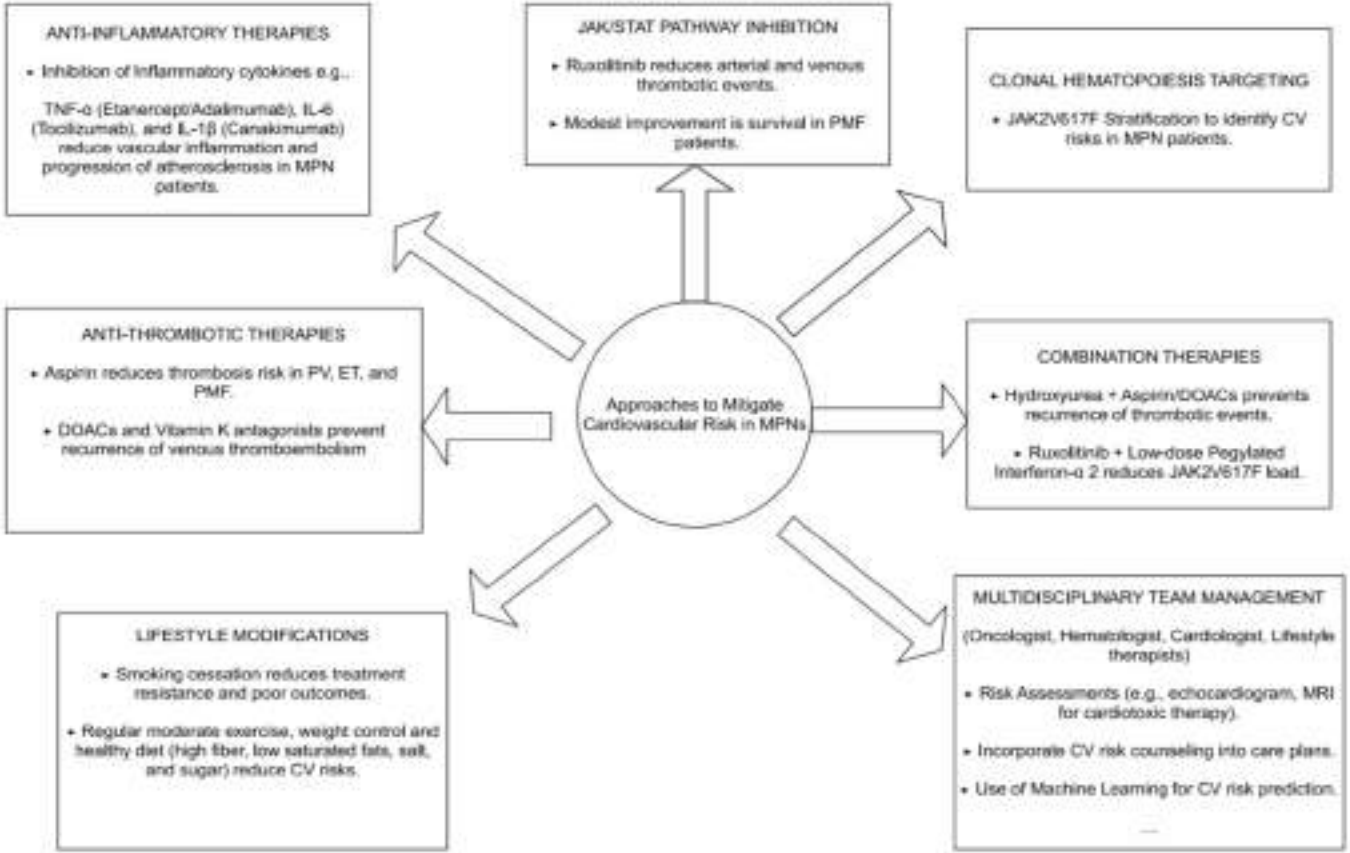


Crizanlizumab, a humanized monoclonal antibody that binds P-selectin, which could certainly be of interest in MPN in view of P-selectin **over-expression in JAK2V617F endothelial cells.**

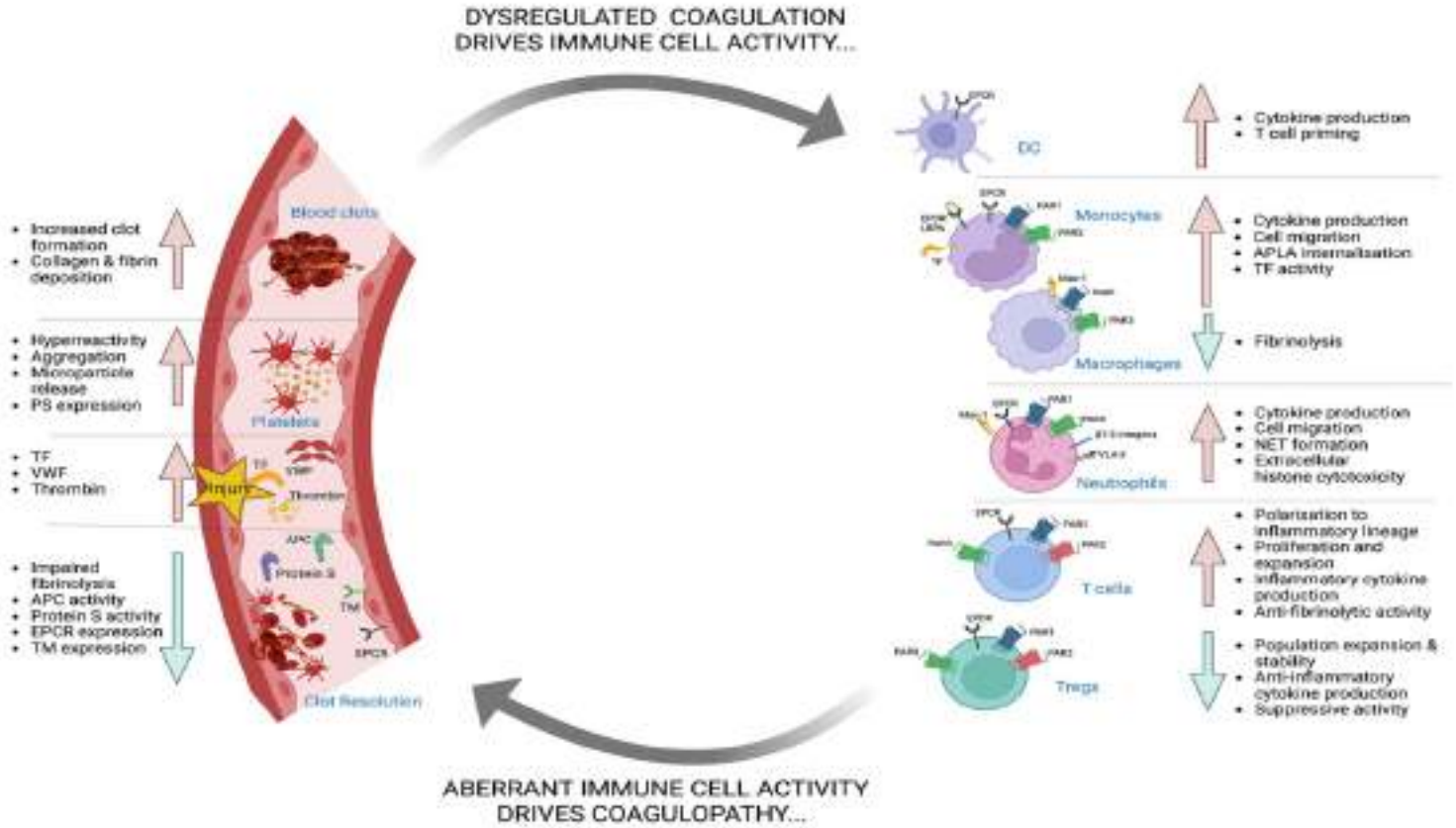
NET formation could be decreased with: (i) ruxolitinib that might directly act on JAK2V617F neutrophils, (ii) aspirin that could inhibit platelet participation in NET formation, (iii) NAC, or (iv) PAD4 inhibitor.

Circulating NETs could be targeted by the administration of DNAse or anti-histones.

Guy A et al. Leukemia 2021



Khan M et al. Discover Medicine 2025



Khan M et al. Discover Medicine 2025