Progetto Ematologia Romagna

Meccanismo oncogenetico dell'infiammazione

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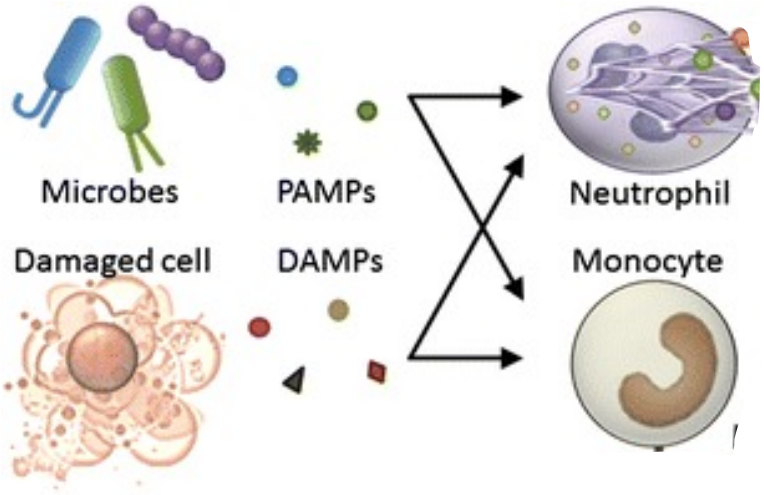
Inflammation

Protective response of the organism to stimulation by invading pathogens or endogenous signals such as damaged cells, thus resulting in the elimination of the initial cause of injury, the clearance of necrotic cells and tissue repair

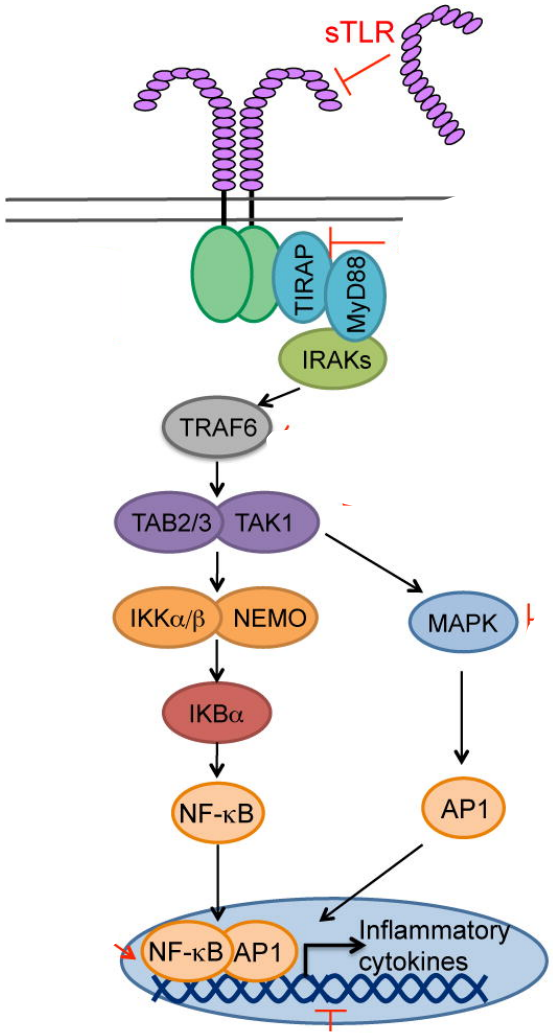


PAMPS (pathogen-associated molecular patterns):

- ✓ cell wall components (LPS, b-glucan)
- ✓ flagellar components (flagellin)

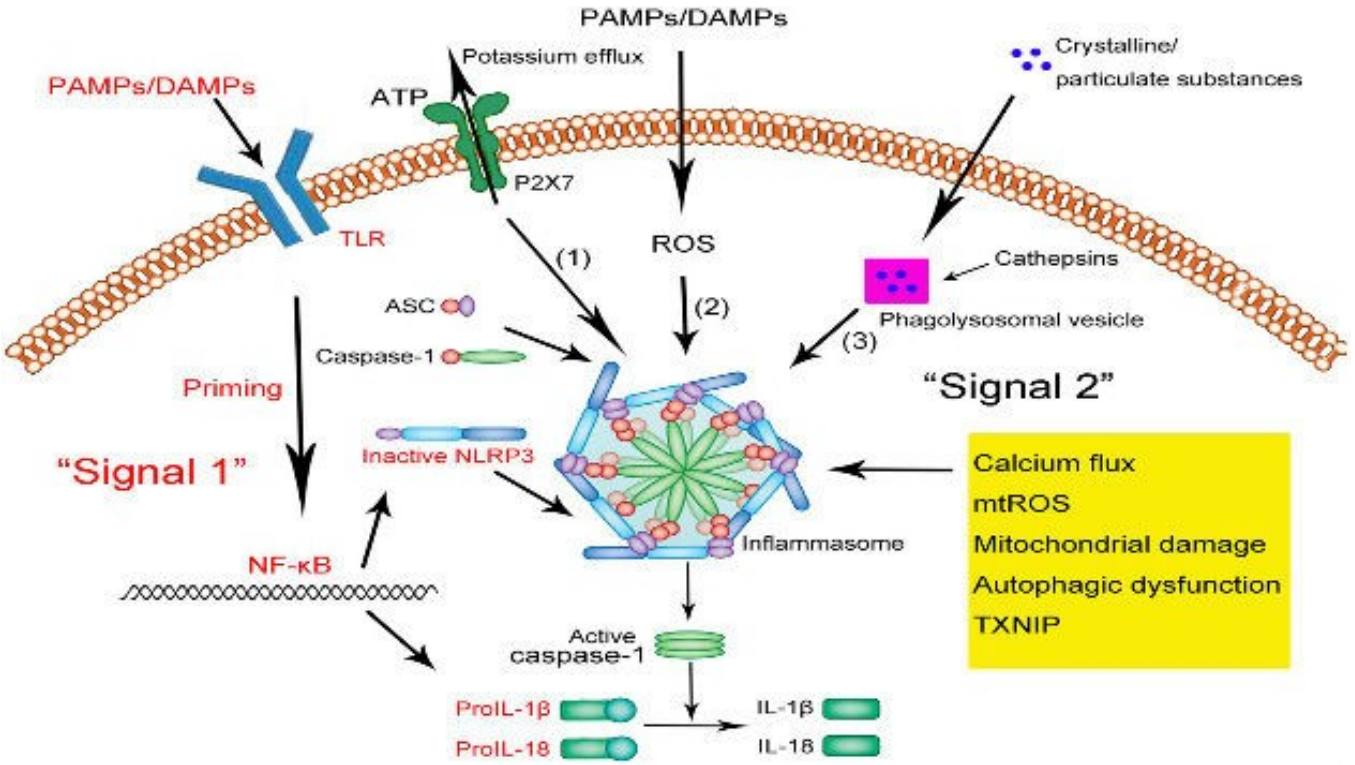
DAMPS (danger-associated molecular patterns)

- ✓ Nuclear proteins (HMGB1), histones
- ✓ Purine metabolites such as ATP
- ✓ Uric acid
- ✓ Mithocondrial components (formyl peptides, mithocondrial DNA)



Germline-encoded pattern-recognition receptor (PRR)

TLR = Toll-like receptor
AP-1 = Activator protein-1



Inflammasome

Inflammation key elements

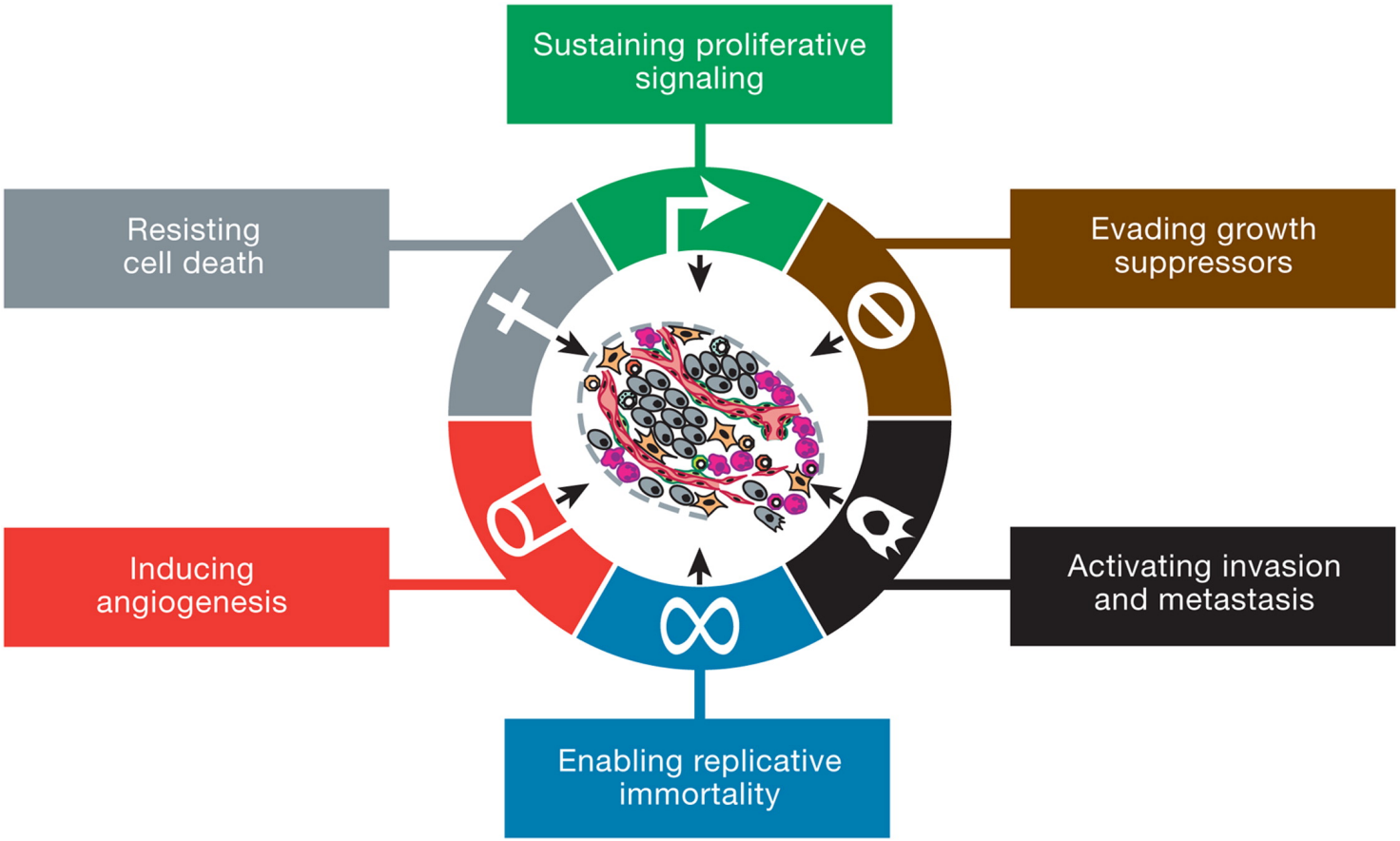
Chemical mediators

- ✓ Cytokine
- ✓ Chemokines
- ✓ Growth factors

Cells

- ✓ Macrophages
- ✓ Neutrophils
- ✓ T-cells
- ✓ Endothelial cells

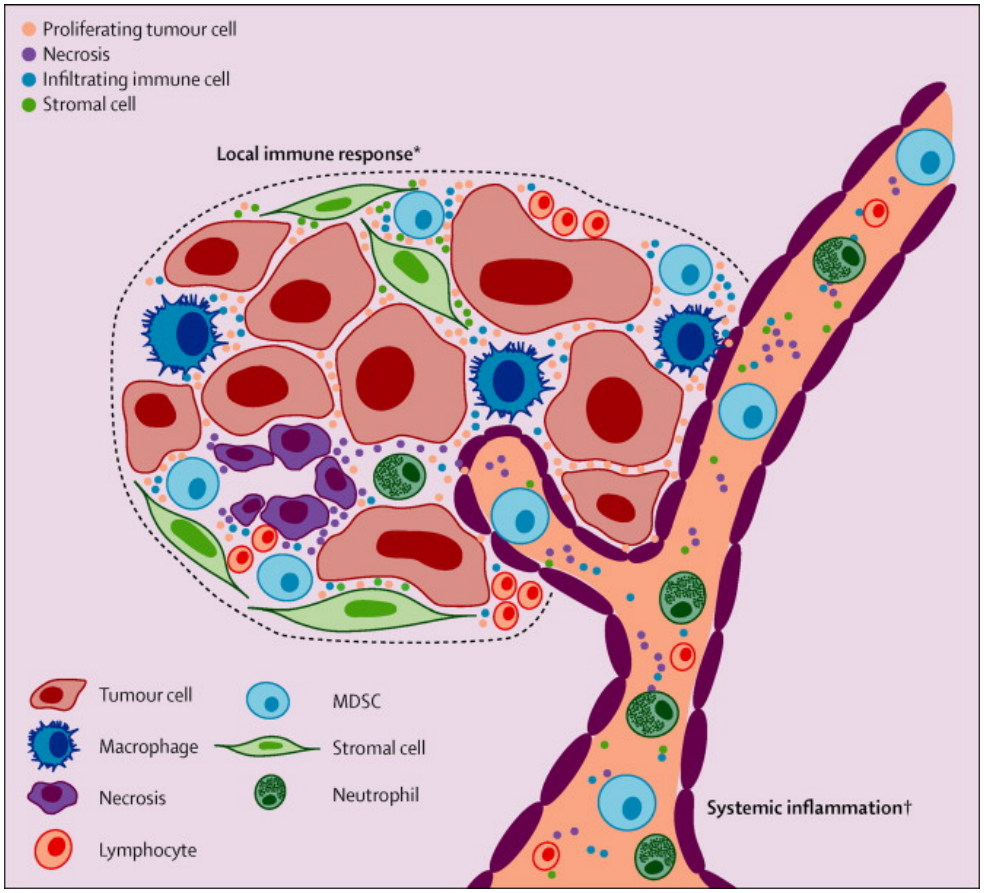
Cancer hallmarks



Mechanisms of cancer-related inflammation

Main characteristic	Main pathways	Specific complications
✓ Infiltration of tumor-associated macrophages with strong immunosuppressive activity	✓ M2 macrophage phenotype ✓ Checkpoint proteins PD-1, PD-L1 and CTLA-4 ✓ IL-1beta, IL-6, TNF, IL-4, IL-10, TGF-beta ✓ Pentraxin-3	✓ T cell exaustion and anergy ✓ Tumor progression

Highlights of onco-inflammation



1. Local and systemic dimension of inflammation

Highlights of onco-inflammation

Prognostic use of systemic inflammation

- ✓ Neutrophil count, white cell count, neutrophil/ lymphocyte ratio
- ✓ Glasgow prognostic score; albumin, CRP
- ✓ B symptoms
- ✓ Circulating myeloid derived suppressor cell (MDSC) count

Highlights of onco-inflammation

2. Oncogenesis vs. oncoinflammation

OPEN ACCESS Freely available online

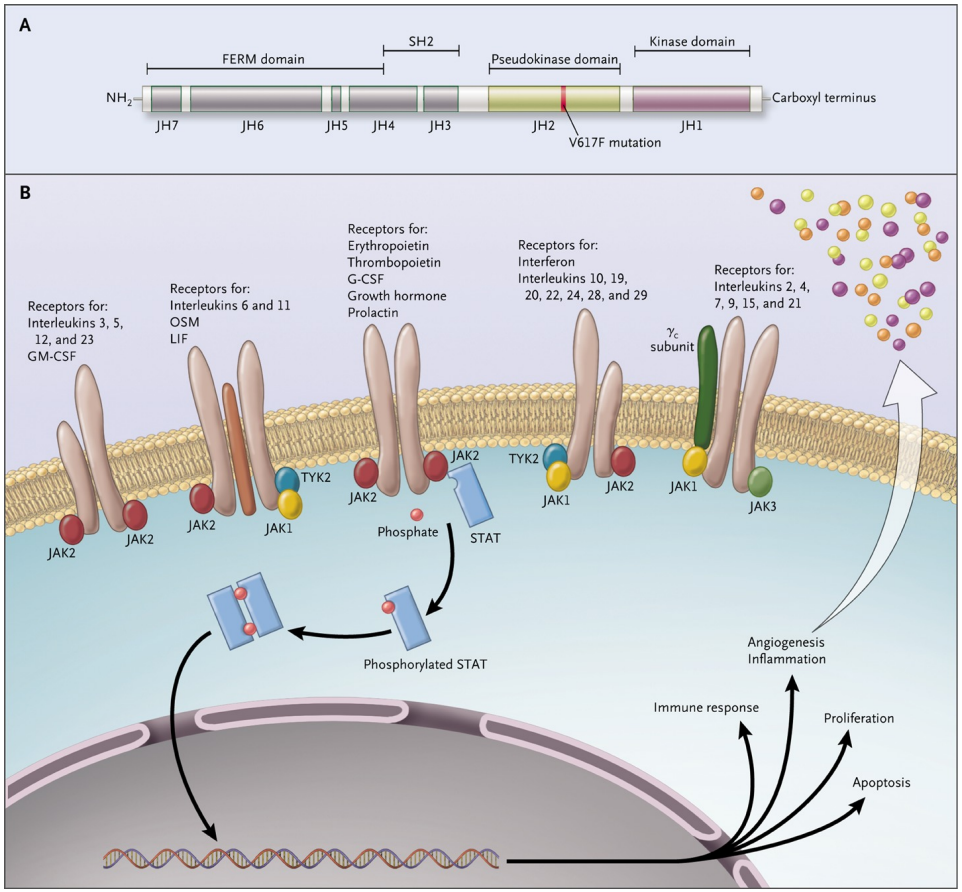
PLOS | ONE

Molecular Profiling of Multiple Human Cancers Defines an Inflammatory Cancer-Associated Molecular Pattern and Uncovers KPNA2 as a Uniform Poor Prognostic Cancer Marker

Saleh M. Rachidi[1,2], Tingting Qin[3], Shaoli Sun[4], W. Jim Zheng[3,5], Zihai Li[1,2]* 2013

Gene expression data revealed an inflammatory signature shared by seven epithelial cancer types.
Onconflammation is a driver of for oncogenesis.

Highlights of onco-inflammation



2. Oncogenesis
vs.
oncoinflammation

Highlights of onco-inflammation

2. Oncogenesis vs. oncoinflammation

OPEN

Leukemia (2018) **32**, 438–449

www.nature.com/leu

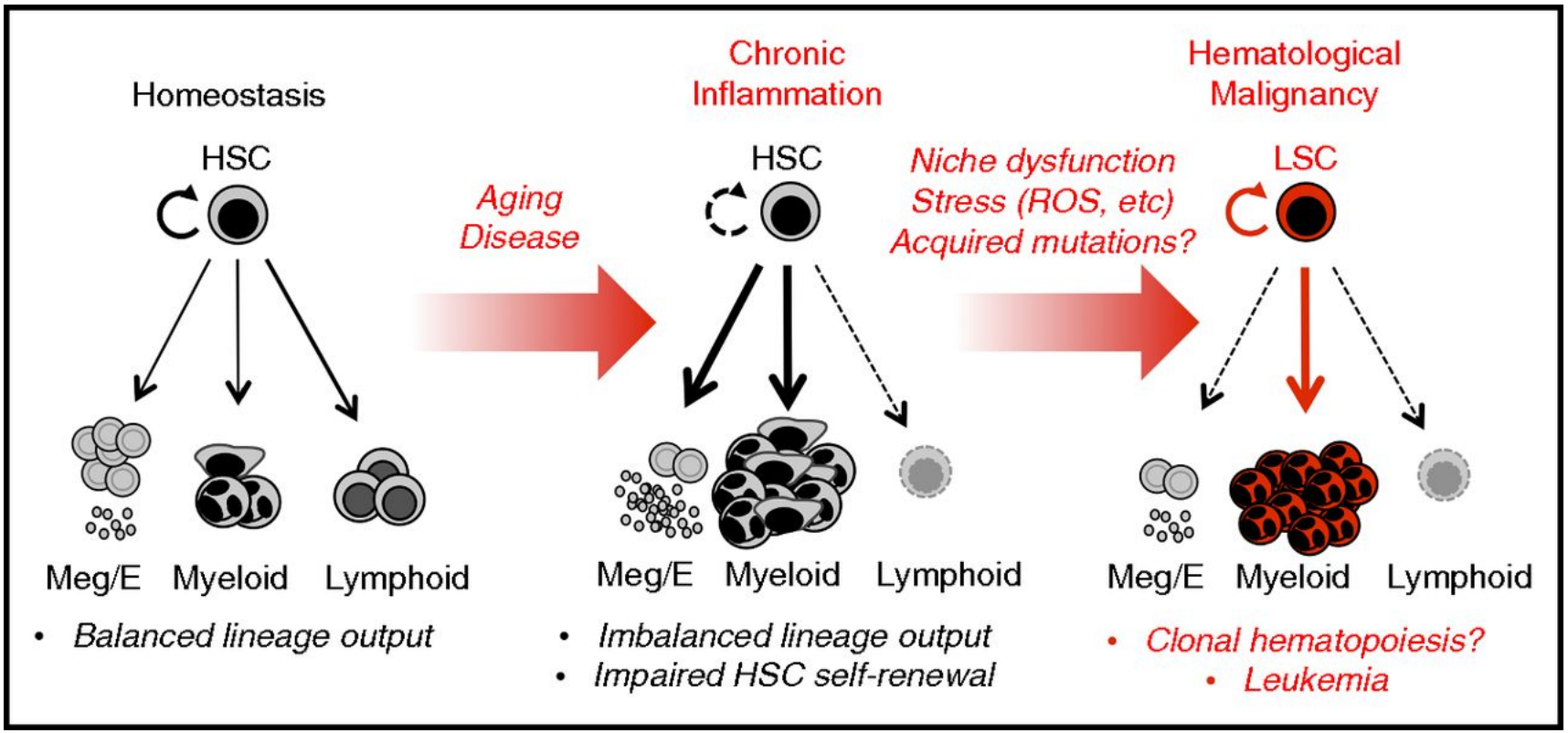
ORIGINAL ARTICLE

Involvement of MAF/SPP1 axis in the development of bone marrow fibrosis in PMF patients

S Ruberti[1,10], E Bianchi[1,10], P Guglielmelli[2], S Rontauroli[1], G Barbieri[1], L Tavernari[1], T Fanelli[2], R Norfo[1,3], V Pennucci[1], G Corbizi Fattori[2,4], C Mannarelli[2,4], N Bartalucci[2], B Mora[5], L Elli[5], MA Avanzini[6], C Rossi[1], S Salmoiraghi[7], R Zini[1], S Salati[1], Z Prudente[1], V Rosti[8], F Passamonti[5], A Rambaldi[7], S Ferrari[9], E Tagliafico[9], AM Vannucchi[2,11], R Manfredini[1,11] on behalf of the AGIMM (AIRC Gruppo Italiano Malattie Mieloproliferative) Investigators

Highlights of onco-inflammation

3. Age/inflammation determine the fate of HSCs



Highlights of onco-inflammation

3. Age/inflammation determine the fate of HSCs

Leukemia Research 60 (2017) 18–23

Contents lists available at ScienceDirect

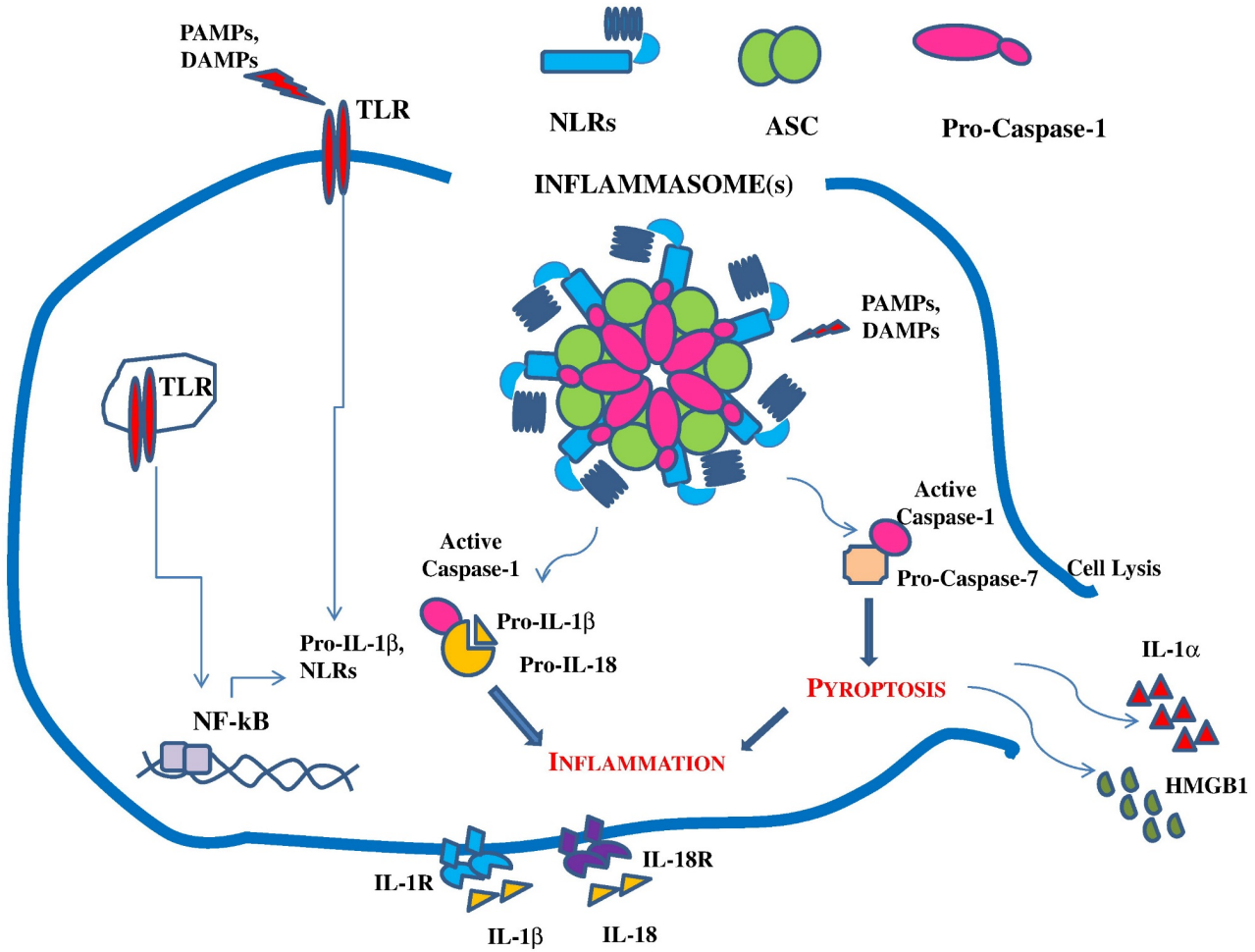
Leukemia Research

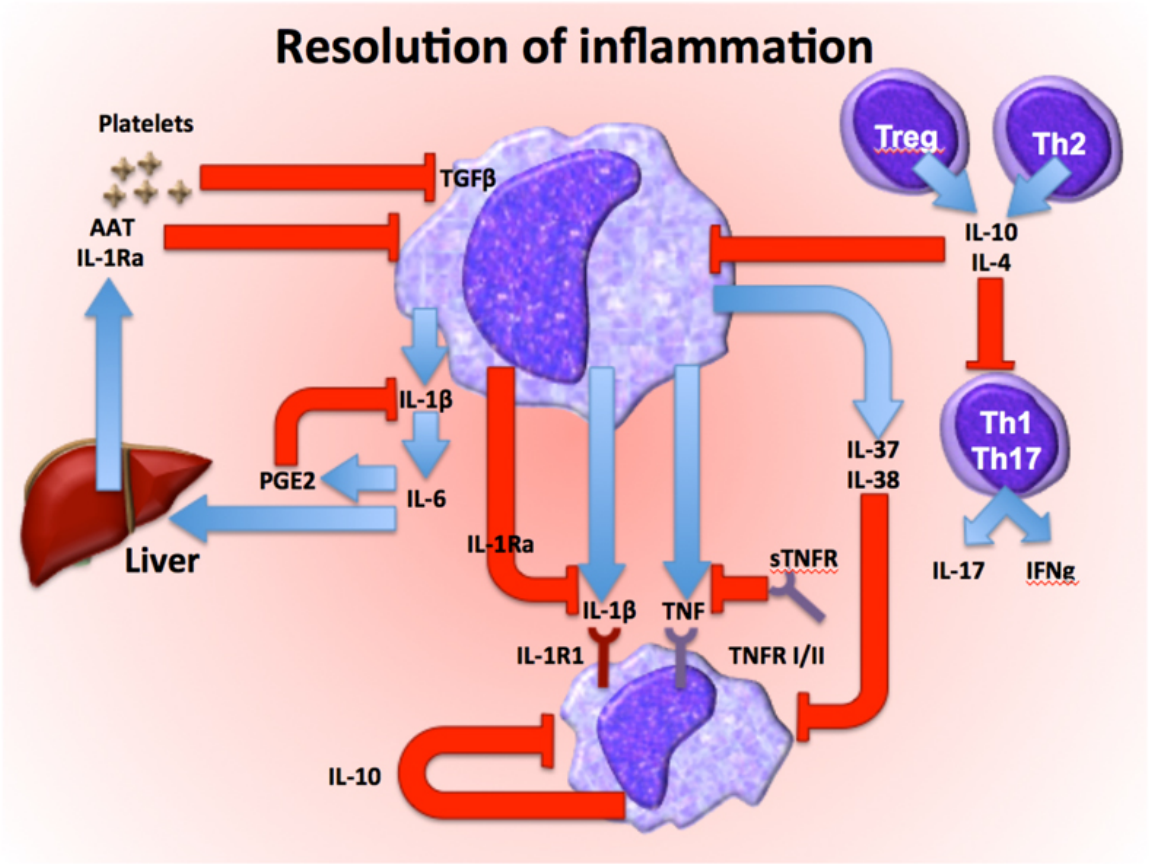
journal homepage: www.elsevier.com/locate/leukres

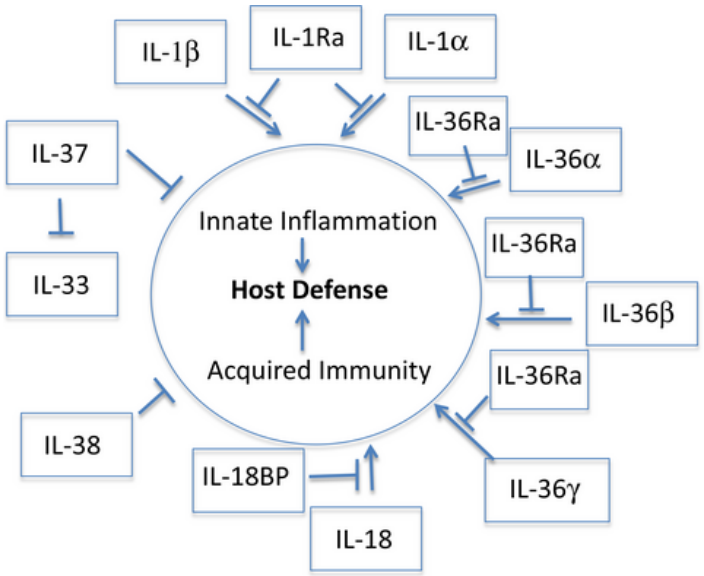
Research paper

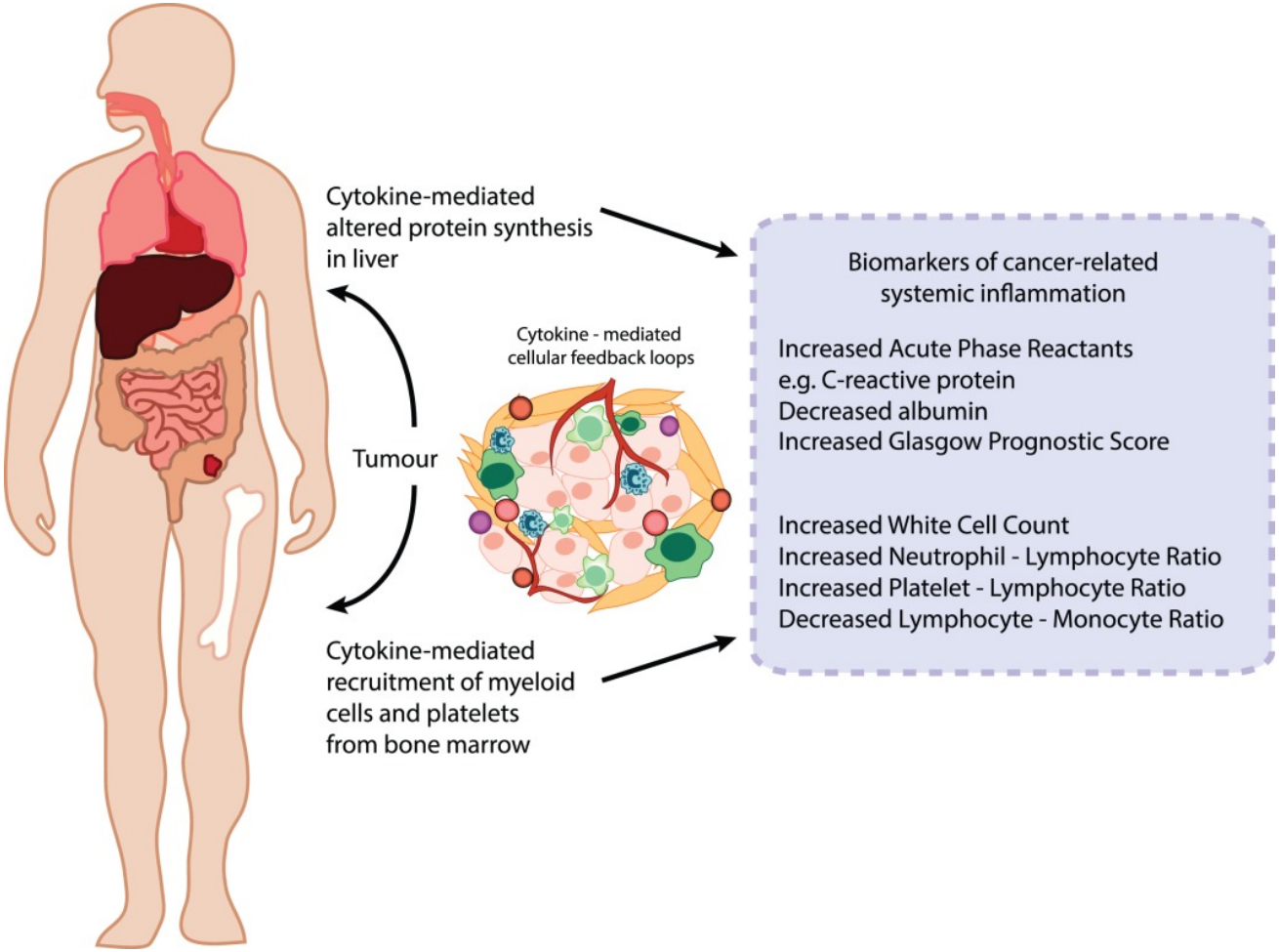
Primary myelofibrosis: Older age and high *JAK2*V617F allele burden are associated with elevated plasma high-sensitivity C-reactive protein levels and a phenotype of progressive disease

Giovanni Barosi[a,*], Margherita Massa[b], Rita Campanelli[a], Gabriela Fois[a], Paolo Catarsi[a], Gianluca Viarengo[c], Laura Villani[a], Valentina Poletto[a], Tiziana Bosoni[d], Umberto Magrini[a], Robert P. Gale[e], Vittorio Rosti[a]


PAMPs,
DAMPs
TLR
NLRs
ASC
Pro-Caspase-1
INFLAMMASOME(s)
PAMPs,
DAMPs
TLR
Active
Caspase-1
Pro-Caspase-7
Cell Lysis
Active
Caspase-1
Pro-IL-1β
Pro-IL-18
Pro-IL-1β,
NLRs
NF-kB
PYROPTOSIS
IL-1α
INFLAMMATION
HMGB1
IL-18R
IL-1R
IL-1β
IL-18


Resolution of inflammation
Platelets
TGFβ
AAT
IL-1Ra
Treg
Th2
IL-10
IL-4
IL-1β
PGE2
IL-6
Liver
IL-37
IL-38
Th1
Th17
IL-1Ra
sTNFR
IL-17
IFNg
IL-1β
TNF
IL-1R1
TNFR I/II
IL-10


IL-1β
IL-1Ra
IL-1α
IL-36Ra
IL-36α
IL-37
IL-33
Innate Inflammation
Host Defense
Acquired Immunity
IL-36Ra
IL-36β
IL-36Ra
IL-36γ
IL-38
IL-18BP
IL-18


Cytokine-mediated
altered protein synthesis
in liver
Cytokine - mediated
cellular feedback loops
Tumour
Cytokine-mediated
recruitment of myeloid
cells and platelets
from bone marrow
Biomarkers of cancer-related
systemic inflammation
Increased Acute Phase Reactants
e.g. C-reactive protein
Decreased albumin
Increased Glasgow Prognostic Score
Increased White Cell Count
Increased Neutrophil - Lymphocyte Ratio
Increased Platelet - Lymphocyte Ratio
Decreased Lymphocyte - Monocyte Ratio

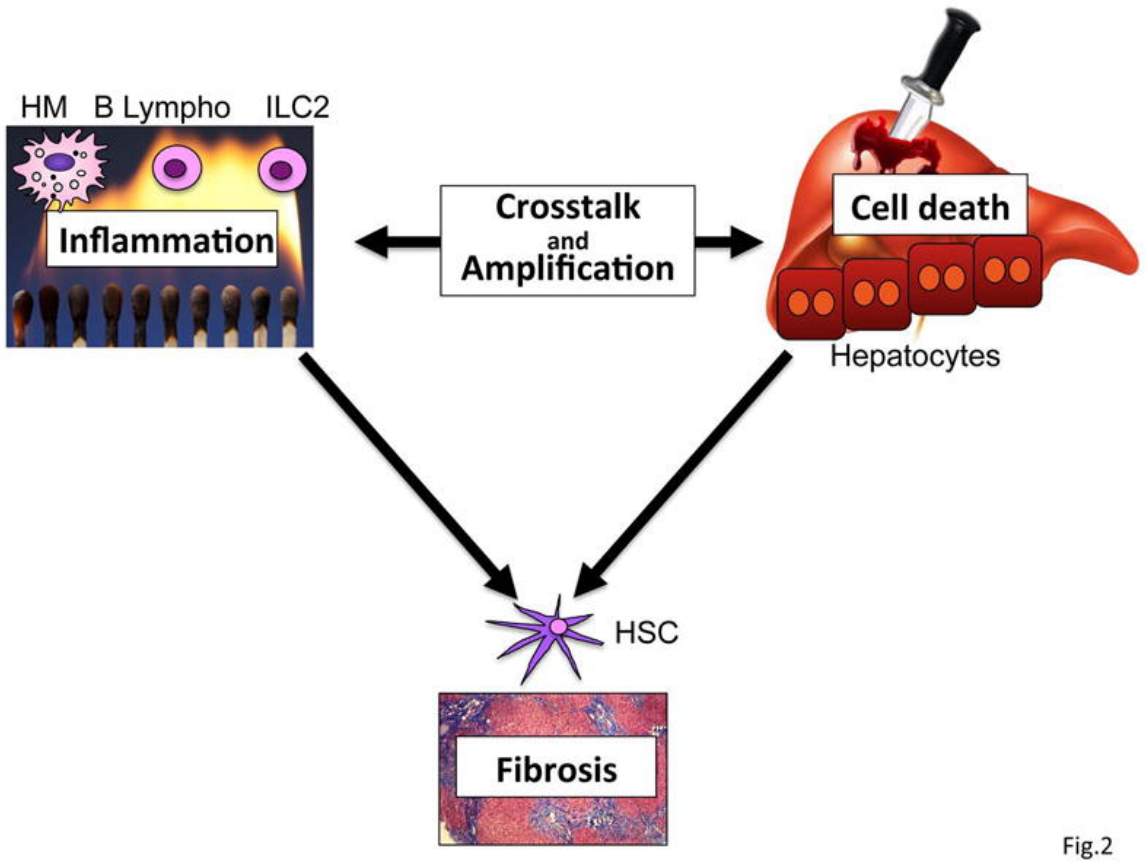
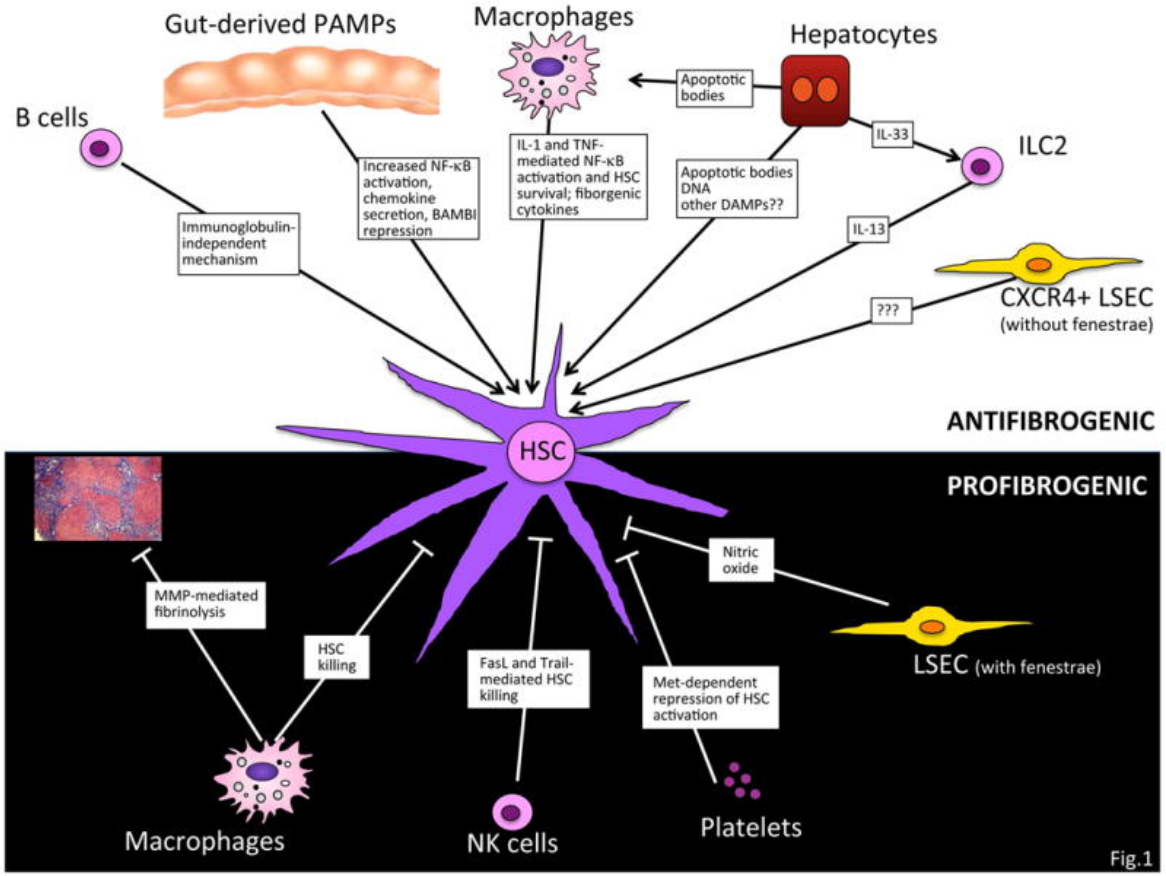
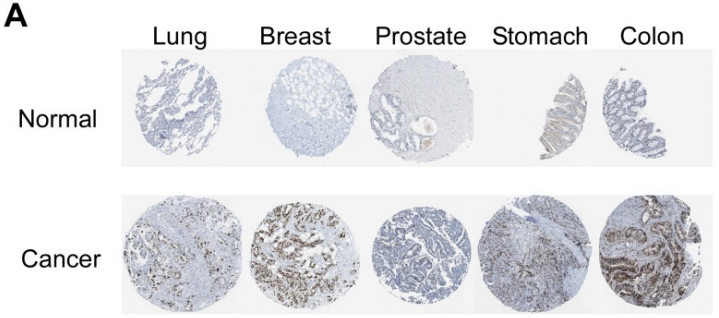

HM B Lympho ILC2
Inflammation
Crosstalk
and
Amplification
Cell death
Hepatocytes
HSC
Fibrosis

Fig.2

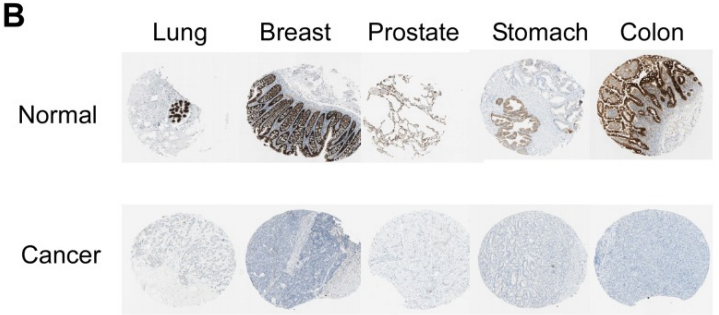

Gut-derived PAMPs
Macrophages
Hepatocytes
B cells
Apoptotic bodies
IL-33
ILC2
Increased NF-κB activation, chemokine secretion, BAMBI repression
IL-1 and TNF-mediated NF-κB activation and HSC survival; fiborgenic cytokines
Apoptotic bodies DNA other DAMPs??
Immunoglobulin-independent mechanism
IL-13
???
CXCR4+ LSEC
(without fenestrae)
ANTIFIBROGENIC
HSC
PROFIBROGENIC
Nitric oxide
MMP-mediated fibrinolysis
HSC killing
FasL and Trail-mediated HSC killing
Met-dependent repression of HSC activation
LSEC (with fenestrae)
Macrophages
NK cells
Platelets
Fig.1

A

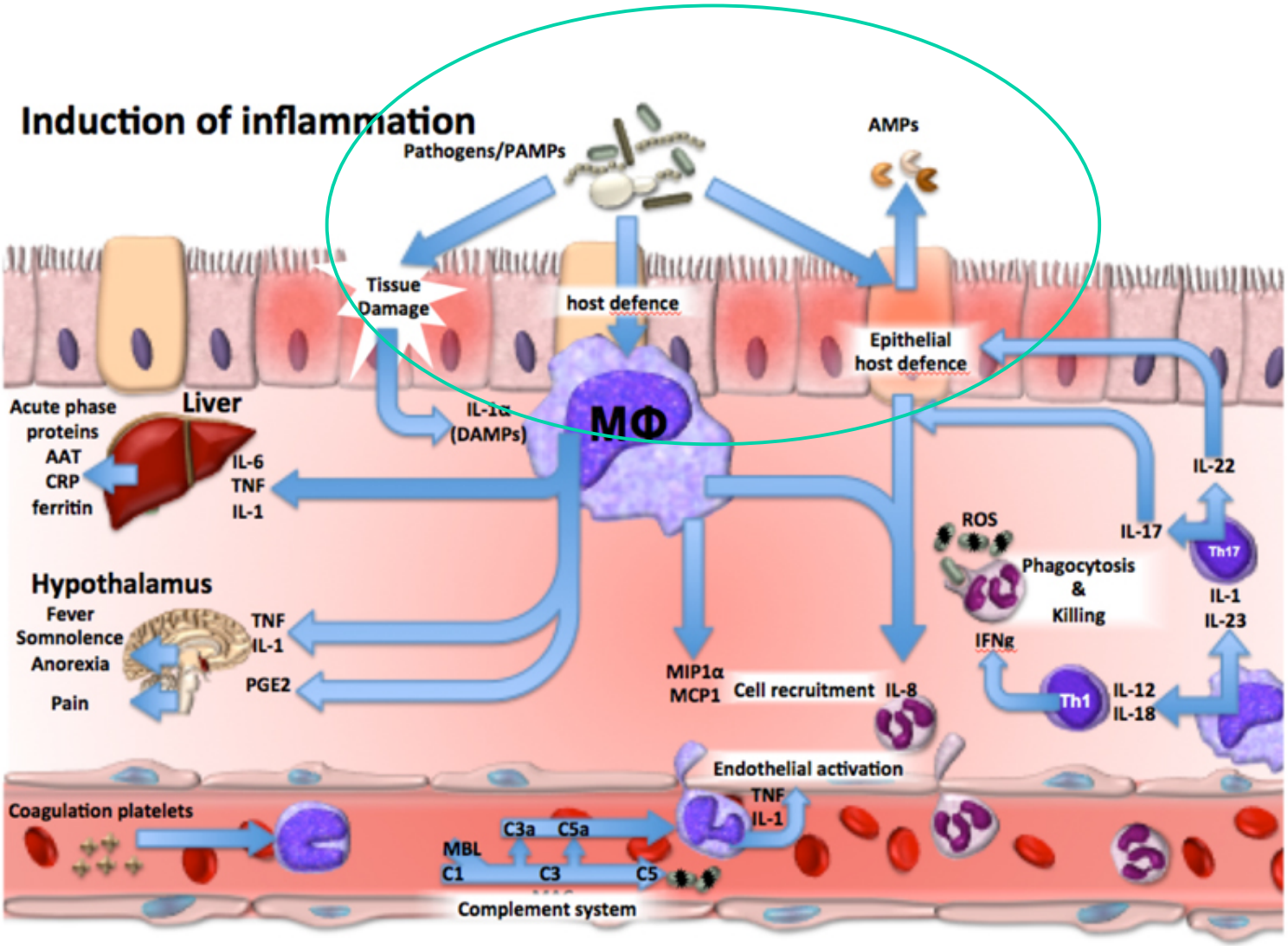


Lung Cancer	Breast Cancer	Prostate Cancer	Gastric Cancer	Colon Cancer	Pancreatic Cancer	Oral Cancer
3.23	2.13	0.99	2.8	2.17	2.45	1.65

B



Lung Cancer	Breast Cancer	Prostate Cancer	Gastric Cancer	Colon Cancer	Pancreatic Cancer	Oral Cancer
0.22	0.47	0.6	0.27	0.55	1.32	0.88


Induction of inflammation
Pathogens/PAMPs
AMPs
Tissue Damage
host defence
Epithelial host defence
Acute phase proteins
AAT
CRP
ferritin
Liver
IL-6
TNF
IL-1
IL-1α (DAMPs)
MΦ
IL-22
ROS
IL-17
Th17
Phagocytosis & Killing
IL-1
IL-23
Hypothalamus
Fever
Somnolence
Anorexia
Pain
TNF
IL-1
PGE2
MIP1α
MCP1
Cell recruitment
IL-8
IFNg
Th1
IL-12
IL-18
Endothelial activation
TNF
IL-1
Coagulation platelets
C3a
C5a
MBL
C1
C3
C5
Complement system