Journal of Autoimmunity xxx (2017) 1–6

Contents lists available at ScienceDirect

Journal of Autoimmunity

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

Inflammation and myeloproliferative neoplasms

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ARTICLE INFO

Article history:
Received 21 June 2017
Accepted 23 June 2017
Available online xxx

Keywords:
Myeloproliferative neoplasm
Inflammation
Mutations
PTX-3
hs-CRP

ABSTRACT

Myeloproliferative neoplasms (MPN) include three main entities: Polycythemia Vera (PV), Essential Thrombocythemia (ET), and Myelofibrosis (MF). MPN represent a unique model of the relationship between the clonal development of a hematologic malignancy and chronic inflammation. The neoplastic clone is the main driver of this inflammatory reaction as demonstrated by the curative effect of allogeneic stem cell transplantation which leads not only to a complete restore of the hematopoiesis, but also to regression of bone marrow fibrosis. The neoplastic clone and its differentiated progeny are also the main source of an indirect paracrine secretion of inflammatory cytokines released by different normal cells present within the tumor microenvironment. In the end, the cytokine storm within the bone marrow niche leads to fibrosis. In addition, chronic inflammation is responsible of the constitutional symptoms which negatively affect the quality of life of MPN patients and represents a major driver for the development of premature atherosclerosis and disease progression. Here we describe the available data about the link between MPN and chronic inflammation in animal models as well as in clinical studies. We also review the practical value of including acute phase inflammatory proteins such as high sensitivity C-reactive protein (hs-CRP) and pentraxin 3 (PTX-3) in prognostic stratification of MPN patients. Interestingly, the plasma levels of these proteins is often increase in MPN patients and this may be important when considering the well-established link between these two inflammatory proteins and the risk of both arterial and venous thrombosis. Although the available drugs are unable to eradicate the malignant clone, the ability to identify patient with a high inflammatory burden and an adverse molecular profile is important to advise therapy with ruxolitinib or even allogeneic stem cell transplantation that currently represents the only potentially curative option for these diseases.

Contents

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http://dx.doi.org/10.1016/j.jaut.2017.06.010
0896-8411/

1. Introduction

Philadelphia negative (Ph-) chronic myeloproliferative neoplasms (MPN) including Polycythemia Vera (PV), Essential Thrombocythemia (ET) and Myelofibrosis (MF), are characterized by the clonal proliferation of an abnormal hematopoietic stem/progenitor cell [1]. The natural history of these neoplasms is marked by frequent thrombotic or hemorrhagic complications as well as a propensity to transform into myelofibrosis (MF) and acute leukemia (AL) [2,3].

The discovery of the Janus kinase 2 (*JAK2*) V617F mutation significantly improved the understanding of the biology of these disorders [4]. The subsequent identification of other acquired somatic lesions, such as *JAK2 exon 12* mutation [5], mutation in the gene encoding thrombopoietin receptor (*MPLW515L/K*) [6] and the recently discovered mutations in the exon 9 of calreticulin (*CALR*) gene [7,8] reinforced the central role of cytokine receptor/signal transduction lesions in promoting MPN phenotypes. In surveys of large MPN cohorts, *JAK2*V617F can be detected in 95% of patients with PV and *JAK2* exon12 mutation in the remaining 5% of patients. Among ET patients *JAK2*V617F can be detected in 60–65% of patients, *MPL*W515L/K in about 5% and *CALR* mutation in about 20%–25%. Very recently, several other mutations have been associated with MPN, including TET2, ASXL1, IDH1/2 and SRSF2 [9]. The understanding that an array of somatic mutations contributes to the biology of these disorders [10,11] prompted new studies to address the impact of patients' mutation background on disease phenotype. These studies demonstrated that somatic mutations can sustain a condition of chronic inflammation [12–14] explaining not only the constitutional symptoms but also the premature atherosclerosis leading to cardiovascular events and the disease progression [3,15–19]. Although the exact roles played by driver mutations is not fully elucidated, the inflammatory microenvironment of MPN [12] [20] seems related to the continuous release of inflammation products from in vivo activated leukocytes and platelets [12–14] and to the accumulation of reactive oxygen species (ROS) in the hematopoietic stem cell compartment [21]. Accordingly, MPN represent disease models of chronic inflammation and cancer [22]. In line with this, use of drugs with anti-inflammatory properties, such as steroids and ruxolitinib, is beneficial to patients due to concurrent reduction in the inflammatory cytokines in plasma [22,23].

In this article, we review the available data about the link between chronic inflammation and MPN and the prognostic role of inflammatory biomarkers in terms of risk of complications as well as disease progression.

2. Cancer-related inflammation

Chronic inflammation is characterized by increased circulating levels of cytokines, chemokines and accumulation of ROS leading to genetic instability which in turn may favor the development of neoplasms and their progression [20]. Although chronic inflammation can be present before a malignant clone develops, most likely it represents a consequence of cancer cell biology. MPN define unique models of the relationship between the clonal development of a hematologic malignancy and chronic inflammation. After the occurrence of one of the key driver mutations, such as *JAK2*V617F, *CALR* or *MPL*, a complex paracrine interaction between inflammatory cytokines and growth factors plays a crucial

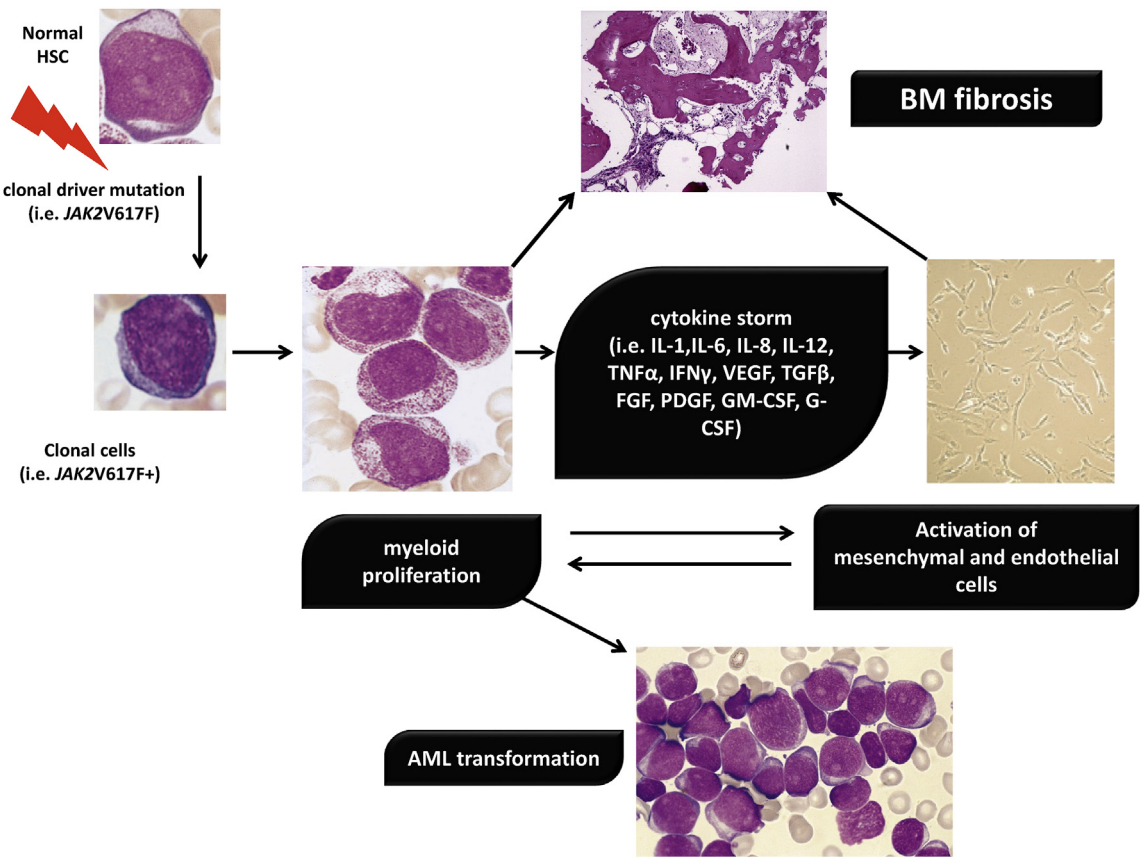

Fig. 1. Interactions between the malignant hematopoietic stem cells and inflammatory cells in pathogenesis of MPN.

Please cite this article in press as: F. Lussana, A. Rambaldi, Inflammation and myeloproliferative neoplasms, Journal of Autoimmunity (2017), http://dx.doi.org/10.1016/j.jaut.2017.06.010