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Review Article

MPNs as Inflammatory Diseases: The Evidence, Consequences, and Perspectives

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In recent years the evidence is increasing that chronic inflammation may be an important driving force for clonal evolution and disease progression in the Philadelphia-negative myeloproliferative neoplasms (MPNs), essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF). Abnormal expression and activity of a number of proinflammatory cytokines are associated with MPNs, in particular MF, in which immune dysregulation is pronounced as evidenced by dysregulation of several immune and inflammation genes. In addition, chronic inflammation has been suggested to contribute to the development of premature atherosclerosis and may drive the development of other cancers in MPNs, both nonhematologic and hematologic. The MPN population has a substantial inflammation-mediated comorbidity burden. This review describes the evidence for considering the MPNs as inflammatory diseases, *A Human Inflammation Model of Cancer Development*, and the role of cytokines in disease initiation and progression. The consequences of this model are discussed, including the increased risk of second cancers and other inflammation-mediated diseases, emphasizing the urgent need for rethinking our therapeutic approach. Early intervention with interferon-alpha2, which as monotherapy has been shown to be able to induce minimal residual disease, in combination with potent anti-inflammatory agents such as JAK-inhibitors is foreseen as the most promising new treatment modality in the years to come.

1. Introduction

Recent studies have provided evidence that the chronic myeloproliferative neoplasms (MPNs), essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF), may be preceded by or accompanied by chronic inflammation and also may imply an increased risk for the development of other cancers [1–3]. In these neoplasms morbidity and mortality are massively influenced by cardiovascular and thromboembolic complications [1, 4, 5]. The advanced myelofibrotic stage is typically characterized by transfusion-dependent anemia, large spleen, severe bone marrow fibrosis, and steadily increasing white blood cell counts or severe pancytopenia and end-stage development of acute leukemia, seen in up to 20% of patients with MF [1, 5]. The incidence of MPNs is low, but the prevalence is high and comparable with lung cancer. In 2005, a unique breakthrough was described by the identification of the JAK2V617F mutation in almost all patients with PV and about half of patients with ET and MF [1]. It is possible to monitor the "tumor burden" when analyzing the *JAK2* allelic burden by qPCR. In 2013 the calreticulin mutations were described in a large proportion of the JAK2V617F negative ET and MF patients [6, 7]. The clinical implications of these mutations are being described elsewhere in this Theme Issue.

Chronic inflammation is an important risk factor for the development of atherosclerosis which occurs prematurely in patients with chronic inflammatory diseases, including rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and type II diabetes mellitus. In these diseases, in vivo activation of leukocytes, platelets, and endothelial cells contributes significantly to the increased risk of thrombosis. The

Professor Hasselbalch in his well-formed academic article about haematological neoplasms and their connection with immunity and its disorders. This comes under the main purpose of connecting tumours in general with immunity disorders which can be the reason or the consequence. This article is directed to his audience of students, scientists and experts in the medical field.

The writing style of this article is critical and the hedging language were taken into consideration as the word “may” for example was used over 45 times in the article, and other modal verbs and clauses were used under the functional classification “Mitigator”.

The cohesion and coherence of this article is significant and appears in every part and in the whole piece of the work served the complexity of the information in the whole article to make it comprehensible unit.

Away from information complexity, the language objectivity and complexity are clear with the passive voice used almost all over the work, short sentence-based paragraphs, and the use of lexical words and variation.

The content of this work is serious clarifying the link between the myeloproliferative neoplasms and immunological process, the organisation of the informations and the ideas from the introduction till the last word of the conclusion is clear and well planed, the article is grammatically error-free, and the academic language which was used accurately, all these features confer the formality on the article.

Finally the scientific merit of any academic article is supported by the sources used, in this article the summarizing of many studies and researches were shown to support the main idea of the article, and by using near 150 references the scientific merit is considerable.

Mohamed Hussam Aswad