Metchnikoff's legacy: the dysplastic nature of innate immunity in myelodysplastic syndromes

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Over a century ago, Metchnikoff's seaside investigations into a eukaryotic organism's response to induced inflammation led to the beginning of our understanding of the innate immune system.[1] The imbalance of the lymphoid/macrophage components of this system in myelodysplastic syndromes (MDS) generates an adverse immunological mileau for the development of autoimmune disorders in this spectrum of diseases. Given the inherent contribution of myeloid and lymphoid cells to innate immunity, it is not unexpected that the dysregulation of these cells has an impact on chronic myeloid clonal blood disorders, particularly MDS.[2] The cytopenias and potential for progression of these disorders are generated predominantly by their immunological abnormalities, inflammatory bone marrow microenvironment, hematopoietic stem cell mutation status and vulnerability to inhibitory cytokines.

Multiple epidemiological and clinical studies have demonstrated an increased incidence (10-30%) of autoimmune and inflammatory disorders in association with MDS,[3-5] ranging from limited hematologic manifestations, such as autoimmune hemolytic anemia and immune thrombocytopenic purpura, to systemic diseases affecting multiple organs, including vasculitis, connective tissue diseases, inflammatory arthritis and neutrophilic diseases.[3-5] Some of these disorders may be associated with adverse outcomes (e.g., vasculitis) or progression of the MDS. Conversely, patients with autoimmune disorders are more likely to develop MDS than are members of the general population.[6]

Studies evaluating the deranged biological processes involving innate immunity which underlie the meshing of these neoplastic and autoimmune/inflammatory diseases have provided important insights into the pathogenesis of their co-occurence. Regulatory T cells (T_{reg}) play a critical role in controlling inflammation and autoimmune disorders[7] and are present at a high frequency in the bone marrow. In lower-risk MDS, the number of T_{reg} was shown to be decreased, thereby potentially permitting the emergence of autoimmune responses, including those directed against the dysplastic clone.[8] In addition, it was separately demonstrated that there are interleukin (IL)-17 producing T cells and elevated serum levels of the pro-inflammatory cytokines IL-7, IL-12, RANTES and interferon-γ in lower-risk MDS. In chronic myelomonocytic leukemia (CMML) and some MDS patients, monocytes demonstrate a strikingly abnormal functional imbalance, comprised of >90% classical type monocytes,[9] which, upon pathogen stimulation, produce high levels of a broad range of cytokines, including granulocyte colony-stimulating factor, IL-10, CCL2, IL-6 and S100 inflammatory proteins. The latter proteins are generated in response to activation of pyroptosis, an inflammasome-mediated process of cell death in myeloid clonal disorders.[2] Increased responsiveness of neoplastic CMML hematopoietic precursor cells to microenvironmental inflammatory cytokines, such as granulocyte-macrophage colony-stimulating factor, has also been demonstrated.

The size of a cell population is orchestrated by apoptosis, an ordered form of programmed cell death, which occurs variably during different stages of a disease trajectory. However, in the clinical setting in which inflammatory disorders occur, pyroptosis generated by activated inflammasomes also contributes substantially to cell death in MDS.[2] Inflammasomes are a class of intracellular poly-protein complexes primarily composed of a sensor, an adaptor protein and an effector.[10,11] The nucleotide-binding domain-(NOD) like receptor NLRP3, is a redox-sensitive cytosolic sensor that recruits the ASC (apoptosis-associated speck-like protein containing a caspase-recruitment domain) adaptor protein. NEK7, a member of the NIMA-related kinase (NEK) family, is implicated in the control of inflammasome effector function.[12] In response to diverse pathogenic stimuli that trigger a cascade of downstream reactions, disordered cellular homeostasis, including mitochondrial dysfunction and toll receptor signaling via reactive oxygen species (ROS) are signals that regulate NEK7-mediated NLRP3 inflammasome activation.[10-12] This interaction in turn causes polymerization of ASC into large cytoplasmic aggregates referred to as ASC specks, permitting docking and activation of caspase-1, which produces mature IL-1β and IL-18 (interferon-γ inducing factor) proinflammatory cytokines that are secreted into the extracellular space as inflammatory effectors of pyroptosis.

In this issue of *Haematologica*, Wang *et al.*[13] describe the presence in plasma of a marker (ASC specks) of pyroptotic cell death generated by activation of the inflammasome within MDS bone marrow cells from patients treated with recombinant erythropoietin and lenalidomide. The authors used confocal and electron microscopy to visualize and flow cytometry to quantify these specks, which are released upon cytolysis and circulate in peripheral blood for extended periods because of their inherent resistance to degradation. They provide data suggesting the potential utility of such measurements to define inflammasome activation, identified by this pyroptotic biomarker (ASC specks) and suggest that this feature, along with assessment of serum erythropoietin levels, may represent a method to detect lower-risk MDS patients whose anemia could benefit from treatment with lenalidomide and erythropoietin. These findings provide a potentially useful approach to clinical assessment of inflammation. However, they require further confirmation, especially regarding their specificity and sensitivity for MDS patients' responsiveness to therapy.

There is a genetic basis for the inflammatory phenomena contributing to some of the clinical conditions associated with MDS. Both germline and somatic mutations have been associated with myeloid-associated inflammatory diseases, including Schwachman-Diamond syndrome, an autosomal recessive inherited disease with bone marrow failure and inflammatory symptoms, and the myeloid-restricted cryopyrin-associated periodic syndrome (CAPS), an autoinflammatory disease related to mutations in the *NLRP3* gene.[14] Polymoprhisms in this gene may play a role in the variable

inflammatory clinical features in MDS patients. *TET2* and splice gene mutations, common in MDS, contribute to inflammatory gene expression in macrophages and are associated with cardiovascular inflammatory comorbidities. Acute leukemic transformation is more frequent in MDS patients with autoinflammatory features than in those without. Recently, a clinically severe autoinflammatory disease associated with MDS and other myeloid disorders termed VEXAS syndrome (characterized by Vacuoles in myeloid precursors, E1-ubiquitinating enzyme abnormal function, X-linked, Autoinflammatory disorders, Somatic mutation) has been ascribed to a somatic mutation in the *UBA1* gene.[15] This disorder has escaped much prior clinical attention since the gene is not captured by most current next-generation sequencing mutation panels.

Treatment of MDS patients wih disordered immunological and inflammatory components has been problematic. For certain associated diseases, such as CAPS and Schnitzler syndrome with NLRP3 activation, IL-1 and IL-1 receptor antagonists have been beneficial in disease management and are now being considered for MDS.[11,12,16] Although some MDS patients with both disease elements may respond to therapy with hypomethylating agents or to antagonists of IL-1 or IL-6 or their respective receptors, these drugs appear to have only temporizing effects in this disease setting; nevertheless, they may be steroid-sparing as an aid to symptom management.[17] Other molecular targets have been evaluated for the treatment of such patients, including inhibition of the Toll receptor or Bruton tyrosine kinase signaling.[2] The more recently discovered NEK7 component of NLRP3 activation may provide a novel target for inhibitors of the inflammasome's upstream effector arm.[12] In addition, given the important role of T_{reg} in controlling inflammation and of their deficiency in lower-risk MDS patients, consideration of T_{reg} usage as a feature of cellular therapeutic approaches for such patients may prove valuable in this neoplastic disease with disordered innate immunity.[18]

Thus, the paper by Wang *et al.*[13] heralds methods to improve understanding of pathogenic mechanisms underlying critical interactions between inflammation and myeloid neoplasia. Such advances should facilitate the development of more effective approaches to the treatment of the dysplastic innate immunity involved in the hemato-inflammatory nature of MDS.

Disclosures

No conflicts of interest to disclose.

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