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Editorial
Metchnikoff’s inflamed legacy: the dysplastic nature of myelodysplastic syndrome’s innate immunity

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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 understanding of the innate immune system1. The imbalance of these lymphoid/macrophage components of this system in myelodysplastic syndromes (MDS) has generated an adverse immunologic milieu for the development of autoimmune disorders in this spectrum of diseases. Given the inherent myeloid and lymphoid cells’ contribution to innate immunity, the impact of dysregulation of these cells is not unexpected for the chronic myeloid clonal hemopathies, particularly the myelodysplastic syndromes (MDS)2. The cytopenias and potential for progression of these disorders have been generated predominantly by their immunologic abnormalities, inflammatory marrow microenvironment and hematopoietic stem cell mutation status and vulnerability to inhibitory cytokines.

Multiple epidemiologic and clinical studies have demonstrated an increased incidence (10-30%) of autoimmune and inflammatory disorders in association with MDS3-5, 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 diseases3-5. Certain 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 the general population6.

Studies evaluating the deranged biologic 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-occurrence. Regulatory T cells (Tregs) play a critical role in controlling inflammation and autoimmune disorders7 and are present in high frequency within the marrow. In lower risk MDS, Tregs were shown to be decreased, thereby potentially permitting the emergence of autoimmune responses, including those directed against the dysplastic clone8. In addition, these authors separately demonstrated IL-17 producing T cells and elevated proinflammatory cytokine serum levels of IL-7, IL-12, RANTES and IFN-γ in lower risk MDS. In CMML and some MDS patients, their monocytes demonstrate a strikingly abnormal functional imbalance, being comprised of >90% classical type monocytes9 which, upon pathogen stimulation, produce high levels of a broad range of cytokines, including granulocyte colony stimulating factor (G-CSF), IL-10, CCL2, IL-6 and S100 inflammatory proteins. The latter proteins are generated in response to activation of pyroptosis, an inflammasome-mediated cell death process in myeloid clonal disorders2. Increased
responsiveness of neoplastic CMML hematopoietic precursor cells to microenvironmental inflammatory cytokines such as GM-CSF in have also been demonstrated.

Cell population size is regularly orchestrated by apoptosis, an ordered form of programmed cell death, variably occurring during differing stages of 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. Inflammasomes are a class of intracellular poly-protein complexes primarily composed of a sensor, an adaptor protein and an effector. 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. In response to diverse pathogenic stimuli which 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. This interaction in turn causes ASC polymerization of large cytoplasmic aggregates referred to as ASC specks, permitting docking and activation of caspase-1 that produces mature interleukin-1β (IL-1β) and IL-18 (interferon-γ inducing factor) proinflammatory cytokines, which are secreted into the extracellular space as inflammatory effectors of pyroptosis.

In this issue of the journal, Wang et al described the presence in plasma of a marker (ASC specks) of pyroptotic cell death generated by activation of the inflammasome within MDS marrow cells of patients treated with recombinant erythropoietin and lenalidomide. The authors used confocal and electron microscopy to visualize and flow cytometry to quantify these specks, that are released upon cytolysis and circulate in peripheral blood for extended periods because of their inherent resistance to degradation. They provided data suggesting the potential utility of such measurements to define inflammasome activation, identified by this pyroptotic biomarker (ASC specks) and suggested 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 for clinical assessment of inflammation. However, they require further confirmation, especially regarding their specificity and sensitivity for MDS patients’ responsiveness to therapy.

A genetic basis for the inflammatory phenomena contributes to some of the integration of clinical conditions associated with MDS. Both germline and somatic mutations have been associated with myeloid- associated inflammatory diseases, including patients with Schwachman-Diamond Syndrome, an autosomal recessive inherited disease with marrow failure and inflammatory symptoms, and the myeloid-restricted cryopyrin-associated periodic syndrome (CAPS), an autoinflammatory disease related to mutations in the NLRP3 gene. This gene’s mutation polymorphisms 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 was more frequent in MDS patients with autoinflammatory features than 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 \textit{UBA1} gene\textsuperscript{15}. This disorder has escaped much prior clinical attention since the gene has not been captured by most current NGS mutation panels.

Treatment of MDS patients harboring such immunologic and inflammatory components has been problematic. For certain associated diseases, such as CAPS and Schnitzler syndrome with NLRP3 activations, the IL1 and IL1 receptor antagonists have been beneficial in disease management and are being considered for MDS\textsuperscript{11,12,16}. Although a portion of MDS patients with both disease elements may respond to therapy with hypomethylating agents or to antagonists of IL1 or IL6 or their respective receptors, these drugs appear to have only temporizing effects in this disease setting albeit they may be steroid-sparing as an aid to symptom management\textsuperscript{17}. Other molecular targets have been evaluated for treating such patients, including inhibition of toll receptor or Brution tyrosine kinase signaling (reviewed in reference 2). The more recently discovered NEK7 component of NLRP3 activation may provide a novel target for inhibitors of the inflammasome’s upstream effector arm\textsuperscript{12}. In addition, given the important role of regulatory T cells for controlling inflammation and of their deficiency in lower risk MDS patients, consideration of Treg usage as a feature of cellular therapeutic approaches for such patients may prove valuable in this neoplastic disease with disordered innate immunity\textsuperscript{18}.

Thus, the Wang et al paper\textsuperscript{13} heralds methods to improve understanding of pathogenetic mechanisms underlying critical interactions between inflammation and myeloid neoplasia. Such advances should provide a means toward more effective therapeutic approaches for the dysplastic innate immunity involved in the hemato-inflammatory nature of MDS.

References