Itchy mast cells in MPNs

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In this issue of Blood, Ishii and colleagues investigate the role of mast cells in the pathogenesis of pruritus in patients with MPNs.

The BCR-ABL–negative myeloproliferative neoplasms (MPNs) of polycythemia vera (PV), essential thrombocytopenia (ET), and primary myelofibrosis (PMF) are characterized by a predisposition to thrombosis and hemorrhage, risk of blastic transformation, and premature death. In addition to these serious consequences, myeloproliferative disorder patients suffer variable constitutional symptoms, such as fatigue, bone pain, night sweats, and pruritus. Data gathered from 1179 MPN patients reported that 81% suffer from pruritus, and this symptom was present in 72%, 84%, and 85% of ET, PMF, and PV patients, respectively.1 The intensity of the pruritus can be severe, frequently exacerbated by water (ie, aquagenic pruritus), and has led some patients to discontinue bathing or to commit suicide in intractable cases. Therapy of MPN pruritus has been empiric, with antihistamines sometimes providing relief. Additionally, the use of selective serotonin reuptake inhibitors has been helpful,2 and has suggested that platelets (the repository for serotonin in the blood) may have a role in MPN pruritus.

The pathogenesis of constitutional symptoms and particularly pruritus in MPN remains uncertain, despite recent insights into some aspects of molecular pathogenesis with identification of mutations that affect the JAK–STAT pathway including the JAK2V617F, mutations in the 12th exon of JAK2, and mutations in cMPL.3 Increased JAK2 allele burden has been associated with a greater burden of pruritus among PV patients,4 although the exact mechanism for this association has remained uncertain, with speculation focusing on increased peripheral blood levels of cytokines. Additionally, investigators have investigated the various subsets of leukocytes that might be the way for FLT3 mutations to serve not only as prognostic markers but as potential molecular targets for novel antileukemic therapies.5

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What this study lacks is evidence supporting a causative link between WT1 mutations and the comparatively poor response to therapy. Of particular interest would be evidence at a functional cellular level that WT1 mutational status is associated with parameters that might predict for poor clinical outcome, such as in vitro chemoresistance or differences in apoptotic responses to DNA damage. Such findings might pave the way for WT1 mutations to serve not only as prognostic markers but as potential molecular targets for novel antileukemic therapies.

*** MYELOID NEOPLASIA ***

Comment on Ishii et al, page 5942
Close encounters of the 3D kind

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The small GTPase Cdc42 is a key regulator of cell polarity. In this issue of Blood, Lämmermann and colleagues show that DCs without Cdc42 are still able to migrate fairly efficiently on 2-dimensional surfaces but become irreversibly entangled in 3-dimensional environments, both in vitro and in vivo.

Dendritic cells (DCs) are critical for the initiation of adaptive immune responses by taking up antigen in the periphery, such as skin, to present it to lymphocytes passing through draining peripheral lymph nodes (PLNs). To perform this task efficiently, activated DCs switch their sessile sampling behavior to a highly migratory one, characterized by the acquisition of a polarized phenotype and increased expression of the chemokine receptor CCR7, which responds to its ligands CCL19 and CCL21. These changes are prerequisites for efficient DC migration into different lymphatic vessels, which secrete CCR7 ligands and serve as a communication highway to draining PLNs.

Small GTPases of the Rho and Ras families are key components of the induction and maintenance of a polarized phenotype and migration. Rac and Rho are involved in lamellipodia formation and uropod retraction, respectively. The Rho family member Cdc42 plays a role in induction and maintenance of polarity in various cell types, such as neutrophils and macrophages, in part through stabilization of the leading edge lamellipodia. It remains unclear, however, how Cdc42 affected DC motility.

In this issue of Blood, Lämmermann et al report their findings on the role of Cdc42 during physiologic DC migration obtained in a series of elegant in vitro and in vivo assays. Using primary mouse DCs derived from Cdc42-deficient bone marrow cultures, the authors investigate the migratory properties of these cells on 2-dimensional surfaces. Despite defects in maintaining polarity, Cdc42-deficient DCs still managed to migrate toward an increasing concentration of CCL19, with only slightly reduced migration velocities as compared with wild-type DCs (see top panel of figure). The residual migratory capacity was likely due to largely intact Rac-induced spreading and lamellipodia formation. Thus, on 2-dimensional surfaces, Cdc42 was not absolutely required for directed cell motility.

In a second set of experiments, Lämmermann et al examine the importance of Cdc42 during DC migration in geometrically more complex environments, that is, the 3-dimensional fibrillar networks of collagen matrices in vitro and dermis in vivo. Somewhat unexpectedly, DCs lacking Cdc42 were strongly impaired in their directed motility in 3-dimensional environments in vitro (see bottom panel of figure). Similarly, Cdc42-deficient DCs were entirely blocked in their migration from skin to draining PLNs, due to impaired entry into afferent lymphatic vessels. A more detailed morphologic analysis of Cdc42-deficient DCs uncovered that these cells became rapidly entangled within the 3-dimensional meshwork, with multiple protrusions pulling in different directions. Therefore, whereas migration efficiency in absence of Cdc42 was partially rescued due to the “lack of alternative routes” on 2-dimensional surfaces, cell motility in 3-dimensional environments absolutely required Cdc42.

Although the function of Cdc42 in other leukocytes was not addressed in this study, recent studies provide solid evidence for a

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