dramatically better clinical outcomes than the other 19 patients (see figure).

Despite these fascinating findings, the exact role of FLT3 mutations in leukemogenesis and how they affect prognosis are still not clear. In the group of 5 patients with the good outcome as described in this paper, did the FLT3 mutations arise as part of the transformation process in a more committed progenitor cell (much like 15;17 translocations are thought to occur in acute promyelocytic leukemia), resulting in a more curable disease? Or were they late hits in the progenitor cells of an already established leukemia? Just how deep into the roots of the hematopoietic system do these FLT3 mutations go? ■

REFERENCES

Comment on Pestonjamasp et al, page 2814

Neutrophil chemotaxis: a tail of 2 GTPases

Mary C. Dinauer INDIANA UNIVERSITY SCHOOL OF MEDICINE

A study by Pestonjamasp and colleagues has identified Rac1, a Rho family GTPase, as an important link between the leading edge of migrating neutrophils and their uropod “tail,” via activation of RhoA and myosin.

Polarization of neutrophils in response to chemoattractants results from a complex series of “directional sensing” events leading to remodeling of the actin and myosin cytoskeleton, which are crucial for directed movement of neutrophils into sites of infection or inflammation.1,2 The coordinated and spatially distinct activation of different members of the Rho family of Ras GTPases is critical for this response. At the front of the cell, an actin-rich lamellipodium forms, which requires Rac, Cdc42, and phosphoinositides. At the rear of the cell, the RhoA GTPase regulates myosin-based contraction via Rho kinase and myosin light chain kinase and myosin II.5 The coordinated and spatially distinct activation of different members of the Rho family of Ras GTPases is critical for this response. At the front of the cell, an actin-rich lamellipodium forms, which requires Rac, Cdc42, and phosphoinositides. At the rear of the cell, the RhoA GTPase regulates myosin-based contraction via Rho kinase and myosin light chain kinase and myosin II.5 The coordinated and spatially distinct activation of different members of the Rho family of Ras GTPases is critical for this response. At the front of the cell, an actin-rich lamellipodium forms, which requires Rac, Cdc42, and phosphoinositides. At the rear of the cell, the RhoA GTPase regulates myosin-based contraction via Rho kinase and myosin light chain kinase and myosin light chain kinase in a structure known as the uropod, and the periodic detachment and retraction of uropod are essential for cell motility. A proposed model for the spatial distribution of these signals into “frontness” and “backness” programs, organized by Rac and Rho, respectively, has been proposed by Bourne and colleagues (reviewed in Fenteany and Glogauer,3 Keymeulen et al,3 and Wong et al). In this model, mutual negative feedback occurs, with Rac acting at the front of the cell to locally suppress Rho activation and uropod formation at the leading edge, and vice versa, thus establishing and maintaining polarity.

In the study by Pestonjamasp and colleagues, several approaches were used to show that communication between Rac and Rho to generate neutrophil polarity is more than simply a mutual antagonism. The results suggest that Rac, in particular the Rac1 isoform, also activates RhoA and myosin at the trailing edge of chemoattractant-stimulated neutrophils. The effects of activated or dominant-negative GTPases introduced into human neutrophils were analyzed, complemented by studies using murine neutrophils genetically deficient in either the Rac1 or Rac2 GTPases. Previous studies had shown that the closely related Rac isoforms present in neutrophils, Rac1 and Rac2, play different roles in regulating chemoattractant–induced changes in neutrophil polarity. Neutrophils from Rac2-null mice have impaired chemotaxis due to a marked defect in lamellipodia formation, whereas neutrophils lacking Rac1 form multiple unstable lamellipodia and develop an elongated morphology due to a uropod retraction defect.1,2 In the current study, the introduction of dominant-negative Rac or dominant-negative Rho into human neutrophils produced a phenotype similar to Rac1-deficient mouse neutrophils. Additional studies showed that Rac, particularly Rac1, activity was coupled to Rho activation, which in turn was critical for myosin II contractility, tail retraction, and chemotaxis. Although genetic deletion studies in the murine system allow a relatively clean assessment of the relative functions of these 2 Rac isoforms, whether Rac1 plays a distinct role in regulating RhoA and uropod formation in human neutrophils remains unresolved. The amounts of Rac1 and Rac2 are similar in mouse neutrophils, whereas only 5% to 10% of the total Rac in human neutrophils is Rac1, with Rac2 accounting for the remainder. In addition, dominant-negative forms of Rac1 or Rac2 act by binding stably to Rac guanine nucleotide exchange factors to block Rac activation and lack selectivity for a particular Rac isoform.

The Cdc42 GTPase may also provide positive regulatory signals for Rho activation, and F-actin formation in the frontness response may help to limit the distribution of activated Rho.4 The organization of the lipid membrane itself also contributes to RhoA activation.5 A future challenge is to understand how these multiple underlying molecular events are linked to mediate chemoattractant–induced neutrophil polarization and movement. ■

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Mary C. Dinauer