**REFERENCES**


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**Comment on Huang et al, page 111**

**EnABling the immune synapse**

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In this issue of *Blood*, Huang and colleagues reveal new insights into the mechanism by which c-Abl regulates T-cell responses through actin-mediated effects on the immune synapse.

The immune synapse (IS) forms in response to antigen presentation and T-cell receptor engagement. Following stimulation, components critical for transmitting the activation signal downstream assemble and orchestrate the events required for proper T-cell response. One key step in this process involves reorganization of the actin cytoskeleton and formation of actin-rich signaling complexes. This process requires WAVE2 and HS1, among other molecules; defects in these proteins impair the response. Thus, understanding the way in which these molecules are regulated will illuminate the way T-cell responses are generated.

The knowledge that tyrosine phosphorylation of HS1 is required for its ability to promote actin polymerization at the IS, and that c-Abl kinase activity is important for IL-2 production, an important consequence of T-cell activation, led Huang and colleagues to explore the link between c-Abl and formation of the IS. c-Abl, the tightly regulated protein tyrosine kinase that is aberrantly expressed as a Bcr fusion in chronic myelogenous leukemia (CML), has been implicated in a wide range of cellular functions. Unlike its oncogenic Bcr/Abl counterpart, c-Abl shuttles between the cytoplasm and the nucleus and influences proliferation, survival, the DNA damage response, and other processes. However, despite the long-standing observation that the immune response is impaired in c-abl-null mice, a clear understanding of the mechanisms underlying this impairment has been slow to emerge.

By using imatinib, a drug that inhibits c-Abl activity and shRNA, the authors demonstrate that c-Abl interacts with HS1 and that c-Abl kinase activity enhances HS1 phosphorylation and proper formation of the IS. Interestingly, HS1 phosphorylation by ZAP-70, another regulatory molecule that affects IS formation, is not affected by c-Abl, highlighting the importance of multiple phosphorylation steps in achieving proper regulation. Using video microscopy, the authors reveal that c-Abl affects the IS in a second way. Unlike HS1-deficient cells, in which actin-rich structures disassemble quickly, c-Abl-deficient cells were compromised in spreading and formation of lamellipodia. These defects appear to involve effects on WAVE2, which fails to localize correctly when c-Abl activity and expression are suppressed.

In addition to making important contributions to our understanding of the regulation of IS formation, these experiments raise a number of intriguing questions. For example, do independent signals trigger phosphorylation of HS1 by ZAP-70 as opposed to c-Abl? Perhaps ZAP-70–mediated phosphorylation of HS1 allows the c-Abl SH2 domain to bind to HS1, thereby facilitating c-Abl–mediated phosphorylation of another residue on HS1, allowing the molecule to fully participate in IS formation. Although WAVE2 is crucial for actin polymerization and IS formation, whether c-Abl exerts its effect through direct interaction or through interaction with another component of the WAVE complex requires additional work. c-Abl deficiency also affects chemokine-induced T-cell migration, and discovering whether this phenomenon reflects effects on HS1 or WAVE2 or other molecules should provide a clearer understanding of the mechanisms involved in chemotaxis. Lastly, and perhaps most intriguingly, this work raises the possibility that complications with infection seen in imatinib-treated CML patients stem from inhibition of c-Abl and an impaired T-cell response.

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**Comment on Qiang et al, page 196**

**MM-induced osteolysis: partners in crime**

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In this issue of *Blood*, Qiang and colleagues explore in detail the role of Wnt inhibition in the progression of multiple myeloma–induced OBLs.
EnABLing the immune synapse

Naomi Rosenberg