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Journal club

ABL AT THE LEADING EDGE

Knowing the subcellular localization of a protein is essential for understanding its function. When Stradal *et al.* discovered that the ABL1 (also known as c-Abl) binding partner ABL interactor (ABI) is dynamically recruited to the edge of lamellipodia, their publication rightly attracted much attention. ABI is part of the Scar/WAVE complex that regulates the actin-related protein 2/3 (ARP2/3)-dependent nucleation of filamentous actin at the leading edge and, together with ABL kinases, can regulate cell migration and contribute to cancer metastasis when dysregulated. However, although Stradal *et al.* and Michael *et al.* had shown that ABL1 substrates such as ABI, lamellipodin and lamellipodin's binding partner MENA (also known as ENAH) localize to the very edge of lamellipodia, only weak localization of ABL1 itself was observed here.

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An excellent paper by Fujita *et al.* shows two unanticipated results with respect to ABL1 localization in the presence of the ABL kinase inhibitor STI571 (imatinib), which, based on structural data, is thought to keep ABL1 in a closed, autoinhibited conformation. First, green fluorescent protein-tagged ABL1 dynamically localizes to the very edge of lamellipodia, and this is enhanced by STI571. Second, the amino-terminal myristoyl group of ABL1, which is only accessible in the open conformation, is required for this translocation. This suggests that, in contrast to the structural evidence, STI571-bound ABL1 is in an open conformation in living cells. Unlike the study by Stradal *et al.* that showed ABI localization at the edge of lamellipodia, the importance of Fujita *et al.*'s study, which finally visualizes ABL1 here, might have been missed by the cell biology field.

But what accounts for the different STI571-bound ABL1 conformations? In living cells, binding partners of ABL1 at the leading edge, such as ABI, might keep ABL1 in the open conformation when STI571 is inhibiting the kinase domain. The dynamic recruitment of ABL1 to its substrates at the leading edge implicates it as a key regulator of lamellipodia formation. Therefore, 'seeing' what occurs in living cells might open researchers' eyes to the unexpected.

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