The ARP2/3 complex promotes branched actin networks, but the importance of specific subunit isoforms is unclear. In this issue, Galloni, Carra, et al. (2021. J. Cell Biol. https://doi.org/10.1083/jcb.202102043) show that MICAL2 mediates methionine oxidation of ARP3B, thus destabilizing ARP2/3 complexes and leading to disassembly of branched actin filaments.
decided to investigate the possibility that MICAL-induced oxidation of Met293 in ARP3B inhibits ARP3B activity. Fluorescently tagged MICAL2, but not MICAL1, was recruited to vaccinia-induced actin tails at a position relatively distant from the virus itself, similar to the actin-binding protein coronin (8). Down-regulation of MICAL2, but not MICAL1, increased actin tail stability and suppressed the short actin tail phenotype induced by ARP3B overexpression. Using an antibody raised against oxidized Met293, the researchers confirmed that ARP3B oxidation was reduced following MICAL2 knockdown. Recruitment of MICAL2 to actin tails was dependent on coronin IC expression, and silencing of coronin IC resulted in actin filament stabilization and reversal of ARP3B-induced actin tail shortening comparable to MICAL2 knockdown. Thus, coronin IC recruitment of MICAL2 results in ARP3B oxidation on Met293, leading to dissociation of ARP2/3B isocomplexes and consequent actin networks destabilization.

Interestingly, the authors noted that the actin nucleation promoting factor cortactin, which stabilizes ARP2/3-mediated branch points along actin filaments, was required for actin tail destabilization in ARP3B overexpressing cells but was not necessary for localization of coronin IC or MICAL2 to actin tails. One possibility is that cortactin supports local MICAL2-mediated oxidation of ARP3B at branch points to induce filament de-branching, rather than bulk actin filament depolymerization that would result from direct actin oxidation. Since MICAL proteins are directed to specific cytoskeleton locations by interacting with Myosin 5A (9) and Myosin 15 (10), the consequences of MICAL activity on actin cytoskeleton organization and function may be fine-tuned by specific MICAL subcellular localization and interacting partners.

Given that actin binds directly to the catalytic monooxygenase and calpain homology domains of MICAL proteins to increase enzyme activity and promote methionine oxidation, it is not entirely surprising that the actin-related ARP3B protein can be oxidized by MICAL2. However, the location of Met293 in ARP3B is not analogous to the Met44 or Met47 residues of actin, which raises questions regarding the mechanism of ARP3B oxidation by MICAL2. Structural modeling of the MICAL3–actin complex positions the actin loop containing Met44 and Met47 near the enzyme active site (11). ARP3B may interact with MICAL2 differently to bring Met293 close to the active site for direct oxidation, or H2O2 produced by MICAL2 might diffuse and oxidize highly concentrated nearby proteins. If this second possibility were true, then it is also possible that additional protein targets (e.g., coronin 1C, cortactin, additional ARP2/3 subunits) might also be oxidized on Met or Cys residues. Since the effects of MICAL on actin are counteracted via reduction of the oxidized Met residues by the sulfoxide reductase enzyme SelR (12), it remains to be determined if ARP3B can be similarly reactivated.

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Figure 1. **Vaccinia virus surfs on the outside of the cell, forming an actin tail in the cytoplasm that aids its propulsion.** Arp2/3 complex is involved in initiating the branched actin structures and shows slow dissociation from the branches when it is stabilized by the linker protein cortactin. When an Arp2/3 complex containing the ARP3B isoform of ARP3 forms, the dissociation is enhanced, as ARP3B is subject to oxidation by MICAL2, which is recruited to branches by coronin, causing cortactin displacement and rapid branch dissociating leading to shorter actin tails.