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Journal club

THE ACTIN SEED

Science is a game of serendipity, no matter how much we'd like it to be solely determined by effort. Cliché says that luck favours those prepared, of which there is no better example than the discovery of the Arp2/3 complex.

In the early 1990's, the actin field was in search of a *de novo* nucleator. Although actin polymerization is overall energetically favoured, the formation of 'seeds', which are dimers and trimers, is rate-limiting owing to their high dissociation rates. Any factors that could help to bypass this energetic barrier would almost certainly be important regulators of actin polymerization in the cell.

I did not witness the discovery of the Arp2/3 complex, but the story went something like this: Laura Machesky, then a graduate student in Tom Pollard's laboratory at Johns Hopkins, on account of her own curiosity did a 'fishing' experiment using profilin, an actin monomer binder, as the affinity bait. To no one's explanation to date, a big fish — a complex of seven stoichiometric subunits — was reeled in from *Acanthamoeba* extracts (Machesky *et al.*). Two of these subunits were found to have significant homology to actin; they were named actin-related proteins 2 and 3, and the complex was named the Arp2/3 complex. One year later, the Pollard laboratory modelled structures of Arp2 and Arp3 based on their homology with actin, but the paper was boldly prophetic: as Arp2 and Arp3 mostly preserved the actin-like barbed, but not pointed, ends, the Arp2/3 complex could work like a dimeric seed for actin growth in the barbed-end direction (Kelleher *et al.*).

It was an elegant hypothesis without experimental evidence, until 1997 when Matt Welch in Tim Mitchison's laboratory at UCSF fractionated human platelet extracts to purify cytoplasmic factors hijacked by the pathogenic bacterium *Listeria monocytogenes*, to nucleate actin at the bacterial cell surface (Welch *et al.*). The purification identified a protein complex that displayed seven stoichiometric bands on the polyacrylamide gel. It took no time for Welch *et al.* to recognize what they had, although the direct effect of the Arp2/3 complex in promoting actin nucleation was not demonstrated until a year later, when various activators of the complex were discovered. I was a young assistant professor at Harvard in 1996 and heard about the Welch result before it was published, when Mitchison came to do a sabbatical. Coincidentally, yeast genome sequencing was just completed at the time, which helped my students and me to purify the Arp2/3 complex from yeast and begin to apply genetics to studying its cellular function.

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ORIGINAL ARTICLES Machesky, L. *et al.* Purification of a cortical complex containing two unconventional actins from *Acanthamoeba* by affinity chromatography on profilin–agarose. *J. Cell Biol.* **127**, 107–115 (1994) | Kelleher, J. F., Atkinson, S. J. & Pollard, T. D. Sequences, structural models, and cellular localization of the actin-related proteins Arp2 and Arp3 from *Acanthamoeba*. *J. Cell Biol.* **131**, 385–397 (1995) | Welch, M. D., Iwamatsu, A. & Mitchison, T. J. Actin polymerization is induced by Arp2/3 protein complex at the surface of *Listeria monocytogenes*. *Nature* **385**, 265–269 (1997)