Meeting report

Cell motility and the formation of lamellipodia

Louise Cramer

Address: MRC-Laboratory Molecular Cell Biology, University College London, Gower St, London WC1E 6BT, UK. E-mail: l.cramer@ucl.ac.uk

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In eukaryotic motile cells, protrusion of the lamellipodium - a type of cell margin - requires the assembly of free actin monomers into actin filaments at the cell margin. Less well understood, however, is the importance of actin-filament disassembly in this process, and this was addressed in several studies reported at the *American Society of Cell Biology* annual meeting. When filament disassembly in migrating chick fibroblasts is inhibited with jasplakinolide, protrusion of the lamellipodium is rapidly blocked (my own work). In non-migrating chick fibroblasts, there is a delay in the onset of jasplakinolide-induced inhibition of lamellipodia protrusion, during which lamellipodium length increases linearly with no increase in protrusion rate. When cofilin activity, which severs and disassembles filamentous actin, is inhibited in rat carcinoma cells with antibodies (Maryse Bailly, Albert Einstein College of Medicine) or by phosphorylation (Noureddine Zebda, Albert Einstein College of Medicine), lamellipodium protrusion stimulated by epidermal growth factor (EGF) is blocked. These data show that there is coupling between filament disassembly and lamellipodium protrusion in at least two distinct cell types. That this coupling is rapid in migrating fibroblasts may reflect a situation whereby actin filament assembly directly uses free actin monomer derived from filament disassembly in preference to stored monomer. In contrast, slower coupling in non-migrating fibroblasts implies that free actin monomer is instead derived from stored monomer. The situation in the rat carcinoma cells has not yet - as far as I can tell - been assessed. Irrespective of the source of free monomer, the authors of the cofilin work favour a model where the severing activity of cofilin also provides the free 'plus ends' (barbed, or rapidly growing) required for actin filament assembly. Whether severing, or alternate mechanisms of providing free plus ends, such as uncapping pre-existing filaments as is thought to happen in platelets (Kurt Barkalow, Brigham and Women's Hospital), or *de novo* nucleation of new filaments is the more important in any given cell type is not yet established.

Clearly there are many sub-steps in the actin cycle. I speculate that the relative importance of filament disassembly will turn out to depend on cell activity and on spatial regulation of the concentration of actin polymer and monomer pools in cells. In this scenario, cells that are resting with relatively high concentration of stored monomer will upon initial activation of motility preferentially use this store to assemble filaments. This situation is known to be true for platelets, leucocytes and Thyone sperm. In contrast, stored actin that is available for protrusion in cells which are already motile (for example, migrating cells) and have already initially polymerized filaments, may be more limiting and in this case free monomer may preferentially come directly from filament disassembly. With regards to the source of free plus ends in cells, I predict that preferred mechanism will reflect required spatial location of new filament growth, and required filament length. Thus, cells that must turn frequently, such as neurons navigating during development, must be able to reposition the site of new actin filament growth. It is hard to imagine how filament uncapping or severing could achieve this - as these filaments would be in the wrong spatial location - whereas this is easily achievable through *de novo* nucleation. Maintenance of long filaments required, for example, in filopodia, microvilli, and stereocilia can clearly work by uncapping pre-existing filament plus ends. In contrast, filament severing in these structures would destroy required actin organization.