Directional cell migration requires cell polarization and asymmetric distribution of cell signaling. Focal adhesions and microtubules are two systems which are essential for these. It was shown that these two systems closely interact with each other. It is known that microtubule targeting stimulates focal adhesion dissociation. Our recent study shows that focal adhesions, in turn, specifically induce microtubule catastrophe via a biochemical mechanism. We were able to track down one of the focal adhesion proteins paxillin which is involved in this process. Paxillin phosphorylation was previously shown to be the key component in the regulation of focal adhesion assembly or disassembly. Since microtubule catastrophe dynamic differs at the leading edge and cell rear, similar to paxillin phosphorylation levels, we suggest a model connecting asymmetric distribution of focal adhesions and asymmetric distribution of microtubule catastrophes at adhesion sites as a feedback loop.

Cell migration is important for many biological processes. It requires organized asymmetric dynamics of focal adhesions (FAs), sites where cells interact with extra cellular matrix. FAs appear at the leading edge as small transient dot-like structures termed focal complexes (FXs). FX assembly and disassembly is regulated by phosphorylation status of paxillin a major FX protein. Most of FXs form and disassemble rapidly. However, some adhesions mature in a force-dependent manner, into larger late adhesions. This process, involves both an increase in size and change in molecular composition and is accompanied by a reduction in local paxillin phosphorylation. Late adhesions are more stable, immobile and undergo forced disassembly by multiple microtubule targeting events only underneath the approaching cell body or transform into fibrillar adhesions by a Src-dependent mechanism.

Similarly to the leading edge, proper adhesion patterns at the cell rear are also essential. Most trailing adhesions are initiated in protrusions at the rear and flanks of the cell as FX rapidly mature in response to tension and transform into sliding trailing adhesions. The process of sliding is complex. While adhesion proteins coupled with the actin cytoskeleton can be translocated relative to substratum, those that are associated with the membrane are thought to undergo treadmilling within the adhesion site. Treadmilling, which includes disassembly of adhesion proteins at the distal end and reassembly at the proximal end, is accompanied by fusion with new adhesions formed in front of the sliding one. Thus, despite a protein composition similar to late adhesions, sliding adhesions are more dynamic. Not surprisingly, sliding adhesions have high paxillin phosphorylation at the distal end of the adhesion site, indicating very dynamic assembly/disassembly rates.

Several mechanisms have been proposed for the regulation of adhesion turnover (reviewed in ref. 11). However, these have not accounted for the observed asymmetry of adhesion turnover. Understanding this requires examining the connection with another asymmetric intracellular system, the microtubule network. This dynamic network closely interacts with FAs. Microtubules play an essential role in cell migration and polarized distribution of signals within the cell. Multiple microtubule targeting to FA leads to their disassembly both at the leading edge and at the cell rear.

Unlike microtubule growth in other cell regions, growth at its leading edge is persistent, characterized by short periods of shrinkage. Simultaneous observation of microtubules and FAs show that microtubules specifically target adhesion sites. More detailed analysis of microtubule dynamics reveals that FAs are preferable sites for microtubule catastrophes. Although FAs cover only about 5% of cell area more than 40% of catastrophes occur at these sites. The likelihood of microtubule catastrophe is seven times higher when a microtubule grows through a FA rather than through an adhesion-free area and about 90% of microtubules approaching adhesion sites undergo catastrophe. Although most of the catastrophes occur at late adhesions, due to their increased stability and lifespan, there is no difference in efficiency of catastrophe induction between small focal complexes and large rigid late adhesions. As FX do not have dense adhesion or actin plaque, it is likely that microtubule catastrophe is triggered by a biochemical mechanism rather than mechanical rigidity. This is also supported by the fact that mechanical obstacles in a cell do not necessarily cause microtubule catastrophe.
In this model, asymmetric distribution of microtubule catastrophes is tightly linked to asymmetric regulation of FA. Since asymmetric FA dynamics in a cell are critical for organization of the actin cytoskeleton, tensile force distribution and directional cell migration, we conclude that microtubule catastrophes serve as important regulatory events for asymmetric signaling and dynamics of the whole cell (Fig. 2).

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Significance of microtubule catastrophes at focal adhesion sites

Figure 2. Model for asymmetric focal adhesion and microtubule dynamics. Focal complexes at the leading edge either disassemble or mature in response to tension. Microtubules undergo catastrophe both at focal complexes and late adhesions. Late adhesions disassemble in response to multiple microtubule targeting. At the cell rear a microtubule is captured at the proximal end of sliding adhesion and undergoes multiple catastrophes at its distal end, supporting disassembly of this region.

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