Integrin Special Issue

We are delighted to introduce this Special Issue of *Journal of Cell Science*, which features a series of commissioned articles on integrins, the receptors that mediate the interactions of cells with the surrounding extracellular matrix. Integrins are noncovalently bound heterodimers comprising an α- and a β-subunit. A total of 24 heterodimers have been identified and all interact with the actin cytoskeleton – with the notable exception of the integrin α6β4, which is instead connected to the intermediate-filament system. We have selected Commentaries and a Cell Science at a Glance article that highlight the regulation of integrin activity, the signalling properties of these molecules and their function in important cell-biological processes, such as migration and differentiation.

The interaction of integrins with the actin cytoskeleton is not direct, but depends on a series of adaptor molecules including talin, kindlins, vinculin, ILK and PINCH. Talin occupies a prominent place in establishing this linkage, as in the absence of talin the interaction between integrins and the actin cytoskeleton is lost. It appears that all other cytoskeletal molecules are dispensable for linking integrin to the actin cytoskeleton, and their function may primarily be to reinforce and strengthen this interaction (see Harburger and Calderwood, p. 159; Vicente-Manzanares et al., p. 199; Legate and Fässler, p. 187). Talin binds to the cytoplasmic domain of the integrin β-subunit and not only connects the integrin to the actin cytoskeleton, but also has a role in the activation of integrins to a high-affinity form. Furthermore, binding to talin facilitates the clustering of integrins, thereby increasing their avidity for their specific ligands.

The process whereby integrins become activated from within the cell is referred to as inside-out signalling. At the molecular level, this has been shown to lead to a conformational change in the integrins (see Askari et al., p. 165). Recently, kindlins have been identified as participants in integrin activation and may act upstream of talin (see Legate and Fässler, p. 187).

During cell migration, new adhesions have to be established at the leading edge of the cell and existing ones have to be broken at the rear. Therefore, interactions of integrins with the cytoskeleton are dynamically regulated to allow the receptors to switch between a high and a low state of affinity or avidity, providing the cyclic changes in traction that are necessary to allow for migration (see Vicente-Manzanares et al., p. 199). These functions are particularly important for immune cells that have to cross the blood-vessel wall numerous times when patrolling the body (see Evans et al., p. 215).

In addition to inside-out signalling, integrins can transduce mechanical signals from the extracellular environment into specific intracellular biochemical responses (see Puklin-Faucher and Sheetz, p. 178; Harburger and Calderwood, p. 159), a process known as outside-in signalling. Furthermore, through their ability to link the actin cytoskeleton to the plasma membrane, integrins help to organise the interior of the cell, which may influence important signalling pathways that control cell proliferation, apoptosis and differentiation (see Streuli, p. 171). Indeed, specialised adhesion structures, called focal adhesions, are formed in cells upon ligation of integrins. Besides their role in cytoskeletal stabilisation, focal adhesions contain numerous signalling intermediates that serve as platforms for downstream signalling. Other cellular processes that have recently been linked to integrin-mediated cell adhesion include the orientation of mitotic spindles and the behaviour of stem cells and cancer stem cells (see Streuli, p. 171; Pontier and Muller, p. 207). These two processes are interrelated, as the self-renewal and differentiation of stem cells are strongly influenced by the environment, and the orientation of the mitotic spindle determines the environment in which daughter cells are located.

Together, the articles in this issue of *Journal of Cell Science* provide an exciting overview of current integrin research that we are confident will stimulate readers to devise the next generation of experiments in this area.

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Arnoud Sonnenberg (Monitoring Editor) and Fiona M. Watt (Editor-in-Chief)

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