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# Editorial overview: Cell signalling: Signal transduction to the nucleus, cytoskeleton, and organelles

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Filippo G Giancotti is recognised internationally as a pioneer in research on cell adhesion and signalling. His current research aims to elucidate the mechanisms that enable organ-specific metastatic colonisation and to identify biological mediators of these processes that can be targeted therapeutically. Filippo G Giancotti, MD, PhD, is a Professor of Cancer Biology at U.T. MD Anderson Cancer Center. He co-leads the Prostate Cancer Moon Shot™ Program, serves as Scientific Director of the David H. Koch Center for Applied Research of Genitourinary Cancers, and holds the Olla S. Stribling Distinguished Chair in Cancer Research.

## Introduction

The ability of cells to change their behaviour in response to mechanical and chemical cues is one of the most fascinating and universal features of life.

The development of multicellular animals involved the evolution of a series of intercellular signalling pathways that are not found in single-celled organisms. These pathways were discovered largely through *Drosophila* genetics, where mutagenesis screens for developmental mutants identified many components and genetic epistasis experiments placed these components into linear signalling pathways. Since this early work, much progress has been made in understanding the molecular mechanisms of signal transduction in both *Drosophila* and mammalian cells. Notably, cell biological studies in mammalian cells have led to the realisation that the linear signalling pathways identified in *Drosophila* are extensively interconnected and contain negative and positive feed back loops that regulate network dynamics.

Cells have evolved a diversity of signal transduction pathways that are responsible for sensing events at the cell surface and relaying that information throughout the cell. The most common destination for signal transduction cascades is the cell nucleus, where they control the activity of signal-regulated transcription factors and can thus influence entire gene regulatory networks to alter global cell behaviour. A select group of signalling mechanisms directly target the cytoskeleton, enabling rapid spatial and temporal control of cell behaviour, including various forms of cell polarity. Finally, a small number of signalling pathways appear to directly target particular cellular organelles such as the mitochondrion, where they can influence cellular metabolism or cellular life-and-death decision-making. In this issue, leaders in the field provide an update on recent progress in understanding several of the most important cellular signalling mechanisms and some examples of how different pathways can be integrated to determine cell behaviour.

## Signalling to the nucleus: Wnt, Notch, TGFbeta, Hedgehog, Hippo-YAP, p53 & Mondo-Mlx

Melissa Gammons and Mariann Bienz summarise new insights into the Wnt signalling pathway, where several key components have been found to assemble into three large multiprotein complexes to transduce the Wnt signal: The Wnt signalosome (Wnt-Fz-LRP5/6-Dsh) acts by recruiting the entire Axin degradasome (Axin-APC-GSK3-CK1) to the plasma membrane in order to inhibit its ability to phosphorylate and degrade beta-Catenin. Liberated beta-Catenin then binds to the Wnt enhanceosome (TCF-BCL9/Lgs-Pygo-ChiLS-Groucho/TLE) on target gene promoters to displace the

Groucho/TLE repressor and to induce transcriptional activation. These concepts of signalling via multiprotein complexes to induce switch-like behaviour are a common theme among many pathways reviewed in this issue.

Sarah Bray describes progress in Notch signalling, where cleavage of the Notch receptor releases the Notch intracellular domain (NICD), which translocates to the nucleus to bind to target gene promoters in a multiprotein complex (CSL-NICD-Mam) to displace transcriptional repressors (Groucho/TLE) and to activate transcription. Of the many CSL binding sites in the genome, only 1% was found to be occupied in any given cell, suggesting that an open chromatin state is necessary for Notch to activate its target genes, which are different in each cellular context. Some tissue-specific transcription factors (e.g.: Runx in *Drosophila* hemocytes and human T-cell acute lymphoid leukaemia) have been identified to cooperate with Notch signalling to enable context-dependent programming of gene expression.

Caroline Hill examines how signalling by the TGFbeta ligand NODAL is controlled during development. NODAL functions in embryonic development in mammals and other deuterostomes (e.g.: Zebrafish and the frog *Xenopus*) as well as the cnidarian *Hydra*, but appears to have been lost in protostomes such as *Drosophila*. NODAL binds to a dedicated subset of type I and type II receptors to phosphorylate and activate receptor-regulated SMAD2/3 proteins (R-SMADs), which then bind to SMAD4 and translocate to the nucleus to induce gene expression in cooperation with other transcription factors. For example, in *Xenopus* embryos, one such factor is Foxh1, which is complexed with Groucho/TLE repressor until SMAD2-4 complex binding switches it to an activator. In Zebrafish, new results have revealed the temporal and spatial dynamics of NODAL ligand (Ndr1/2) and antagonist (Lefty1/2) production that underlie formation of the SMAD2-4 signalling gradient. The authors then discuss how gene regulatory networks might measure the duration of signalling to enable responses to temporal dynamics.

Ying Zhang elaborates on signalling by canonical TGFbeta, focussing on potential mechanisms for context-dependent regulation of receptor activation and signalling in different tissues. One interesting idea is that mechanical tension acting via binding of the αvβ6 and αvβ8 integrins to LAP (TGF-β pro-peptide) allows latent and inactive TGFbeta in the matrix to become available and active. In addition, Integrin focal adhesions may cluster TGFbeta receptor type I molecules while excluding the type II receptor. Furthermore, in polarised epithelial cells, the spatial distribution of both type I and type II receptors is tightly restricted, and R-SMAD activation may continue to occur while ligand-receptor complexes are in early endosomal compartments.

Christian Siebold and colleagues review how Hedgehog family ligands bind to the Patched (PTC) receptor, which then activates the Smoothened (SMO) multipass transmembrane protein via a mysterious mechanism that is thought to be mediated by a small molecule second messenger. Active SMO inhibits the Suppressor of Fused (SuFu) and Protein Kinase A (PKA) signal transducers to liberate the GLI transcriptional coactivator. New results concerning the structure and function of PTC and SMO are discussed, including the intruiging idea that PTC acts as a cholesterol flippase to enable this endogenous molecule to regulate SMO signalling.

Alex Fulford *et al.* discuss how the Hippo signalling pathway, composed of the core upstream kinase Hippo/MST and downstream kinase Warts/LATS, can be activated by apically localised proteins and inhibited by proteins localising to the adherens junction. Recent work uncovering the ability of this pathway to be mechanically regulated in mammalian cells via Integrins and the actin cytoskeleton is also summarised. Finally, several unanswered questions are highlighted, including the possible role of endocytic trafficking of certain Hippo pathway components, as well as the mysterious mechanism by which the key nuclear effector Yorkie (YAP and TAZ in humans) undergoes nucleo-cytoplasmic shuttling. Elbediwy and Thompson further elaborate on this signalling system, focusing on the evolution of its upstream regulation by cell adhesion receptors (see below).

Stephano Mello and Laura Attardi review signalling via the p53 transcription factor, which responds to various cellular stress signals including acute DNA damage, and acts via downstream gene expression programs to promote cell cycle arrest and DNA repair followed by cell cycle re-entry or apoptosis, depending on the extent of the insult and ensuing damage. Intriguingly, the ability of p53 to mediate an acute response to DNA damage is dispensable for tumour suppression. Rather, the authors argue that this process involves a broad transcriptional program, which maintains genetic and epigenetic stability, restrains de-differentiation, motility and angiogenesis and promotes ferroptosis, a novel form of apoptosis discussed in depth by Gao and Jiang (see below). Further complexity arises from cellular context.

Essi Havula and Ville Hietakangas describe the important discovery of a novel sugar-sensing signalling pathway that acts via the Carbohydrate Responsive Element Binding Protein (ChREBP), also known as MondoB, and its paralog MondoA. Both MondoA and MondoB interact with a partner protein named Mlx to activate transcription. MondoA is highly expressed in skeletal muscle, while MondoB is prominently expressed in liver and adipose tissue. In *Drosophila*, there is a single Mondo protein that mediates the majority of sugar-induced transcriptional responses, including activation of genes