EDITORIAL

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Integrating the signs

Signals to and within the cell are integrated at many levels to facilitate a meaningful outcome. In this issue of *Nature Structural & Molecular Biology*, we present, in conjunction with *Nature Reviews Molecular Cell Biology*, an in-depth look at the mechanisms underlying such integration.

The sun is finally out (at least for those of us in northern climes), and yes, baseball season is upon us and in full swing (think of this as cricket, but on a square pitch). Watch a game of baseball, as well as many other sports, and you might be treated to the sight of grown-ups sending mysterious, sometimes ridiculous hand signals to one another. About half of the signs are nonsense designed to throw the other team off, but at some point in the middle of these elaborate hand gestures, a simple signal says "here comes the play," followed by instructions for what to try next to score a run. And it's no different in basketball: a simple hand signal from the coach, and some predetermined number of people respond by executing a prepared play that (hopefully) results in points being scored. Sometimes there's miscommunication, or one player will respond out of turn, and the results can cost the game.

Many signaling pathways, once drawn as a linear series of sequential arrows, nowadays look like something more akin to a hairball. We knew that this might be the case. Whereas genetic epistasis analyses had the straightforward upstream vs. downstream outcome, the more nebulous 'parallel pathway' category was always there, indicating that, at some level, there was more going on than just the linear, sequential flow of information. More hints of growing complexity came as we saw that some players were on more than one team, with glycogen synthase kinase 3 being but one of a number of examples of factors that moonlight in multiple signal-transduction pathways. Understanding this network of pathways and how the cell responds in a coordinated fashion to instructions sent from the 'coach' remains a major challenge when thinking about signaling. And given that throwing a drug that targets a single factor into this scrum might have unpredictable outcomes and knock-on effects, networks of interactions are also a major issue to consider when exploring therapies targeting particular pathways.

In this issue, *Nature Structure & Molecular Biology* has teamed up with *Nature Reviews Molecular Cell Biology* to present a Focus on Signal Integration (http://www.nature.com/focus/signalintegration). The aim of this Focus is to bring together two Commentaries, an Essay and a series of Reviews that outline at least some of the technical challenges, recent advances and future perspectives when considering integration and coordination in response to signaling events.

When displaying interactions as networks, there are some clear hubs where multiple factors are located, and such scaffolds seem like an ideal venue for coordinating a response. On page 653, Pawson and Scott consider a classic example of such a multiprotein complex 'huddle', the A kinase anchoring protein AKAP-Lbc, and outline other examples where such scaffolded coordination of responses might occur. However, such a huddle is not necessarily directed by a protein. In sports, we acknowledge that intangibles, such as the effect of a supportive home crowd, can impact the outcome of the game. Context cannot be ignored, and on page 659, Groves and Kuriyan discuss the fact that many signaling events are occurring on a substrate with unique biophysical properties: the cellular membrane. Approaches to examining the effect of the membrane, and examples where the membrane has a clear influence on signaling, are discussed. Finally, Dikic and colleagues discuss the effect of post-translational modifications on signal integration. Altering or modifying key players in a pathway is likely to have ramifications through a network of interacting factors, and examples are outlined in this Review on page 666.

Coordination of signaling happens within a cell but also must occur at the level of the organism and in response to the environment, and here we turn to our sessile brethren in the plant kingdom. On page 642, an Essay by Jallais and Chory discusses integration across an organism, proposing the idea that the shade-avoidance response in plants involves coordination of light and plant hormonal signals at the level of the hormone auxin. We have already mentioned the importance of considering signal integration when developing specific inhibitors for research as well as therapy. On page 646 of this special issue, Cole and colleagues consider new avenues for breaking through the opposing team's lines and developing specific drugs that target pathways exploiting basic principles found in many signaling pathways. Finally, and continuing with the idea of the importance of conformation, we consider how it is that a single protein might structurally coordinate multiple downstream targets. Tesmer examines this issue using the G protein–coupled receptors, a class of receptors that are emerging from the dark at the structural level, and their downstream interacting targets as an example.

The current issue of *NRMCB* contains additional Reviews that also explore signal integration: Lim discusses customizing signaling networks, McNeill and Woodgett cover integration during development and Kholodenko, Hancock and Kolch discuss the coordination of signals in space and time. Technical approaches to examining signal integration are discussed by Choudhary and Mann at the level of mass spectrometry, and Dehmelt and Bastiaens discuss imaging as a means of exploring the spatial integration of signaling. In addition, the online component of the Focus contains a library of Articles and Reviews on the general subject of signaling from across the *Nature* journals.

We hope you enjoy reading these pieces as much as we enjoyed commissioning and reading them; and finally, we would like to thank our advisors, contributors and peer reviewers, without whom this Focus would, of course, have been an impossible goal to achieve. ■