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Cell regulation: A time to signal, a time to respond

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The behaviours of living cells are normally controlled by growth factors, cytokines, and other molecular cues *in vivo*, affecting cell division, migration, differentiation, and survival. Specific receptors on the cell surface recognize these cues and mobilize signal transduction networks, which constitute the intracellular machinery responsible for actuating and regulating functional responses. In cancer, certain proteins (oncogenes) are mutated so as to render the cell autonomous from external cues. Consequently, intracellular signalling is robust and uncontrolled, and thus so are cell proliferation, survival, and movement. It is therefore of paramount importance to understand the intricate mechanisms by which signal transduction networks are governed, but the problem is the daunting complexity at the molecular level. Even when considering a single pathway, one must wade through a morass of protein components and post-translational modifications to figure out how it is regulated.

The encouraging news is that considerable progress over the past twenty years or so has resulted in a mature understanding of many signalling pathways. At least conceptually, this simplifies the problem by allowing us to treat pathways as modules, each responsible for the activation of a critical node in the network. Such ‘master regulators’ would include mitogen-activated protein kinases (MAPKs) and other important protein kinases such as Akt. Hence, the notion is that we can reduce the complexity of the problem by splitting it into two parts: one, the convergence of receptor-mediated pathways resulting in activation of a handful of master regulators, and two, the influences of those regulators on cell behaviour. With this paradigm, we can tackle each of the two parts independently and develop quantitative frameworks in which measurements are compared with mathematical models [1]. Thus, it is envisioned that we will be able to predict the effects of molecular interventions in both normal and transformed cells, a prospect that is not lost on forward-thinking drug companies [2].

In this issue of *BioEssays*, Schilling et al. [3] highlight an important fundamental gap in the paradigm outlined above: at some point, one must make the jump from molecules to phenotype. Whereas the molecular world can be described purely mechanistically, i.e., according to physicochemical principles, it is prohibitively difficult to go from signalling to response that way. For example, a mechanistic model of cell growth would need to wholly incorporate gene expression and cell metabolism. The only recourse is a correlative approach [4]. Signalling readouts (focused on presumed master regulators) are measured along

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with cell responses, and then a mathematical relationship between the two may be constructed. But what relationship do we choose? A linear regression is arguably the simplest approach; is that good enough? To a certain extent, the answer has proven to be yes, although the relationships that have been identified incorporate multiple signalling readouts [5]; as one might expect, measurement of a single pathway does not adequately predict the outcome across all stimulation/intervention conditions.

Schilling et al. [3] add a new wrinkle to this discussion, which is the temporal aspect of cell signalling. Activation of a signalling network is dynamic, subject to receptor downregulation and other forms of negative feedback adaptation. Thus, the magnitude of pathway activation typically peaks early before reaching a quasi-steady plateau. Negative feedback in signalling networks has been sucessfully characterized through quantitative measurements and models [6], but then linking the temporal output of such models to cell responses requires hard assumptions about how the cell makes decisions. As articulated by Marshall [7], is it the steady state that matters most, or the peak? If the entire time course is important, how should one weight the signalling magnitudes at different times? Schilling et al. [3] discuss the merits of mathematically representing the kinetics as a time integral, calculated numerically. They explain that a primary challenge with this approach is that one must assume when the integration should be truncated, i.e. when the cell's decision is final. This sort of conjecture highlights the fundamental difficulties we face when trying to simplify complex biology using mathematics.

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