CELL SIGNALLING

Going global

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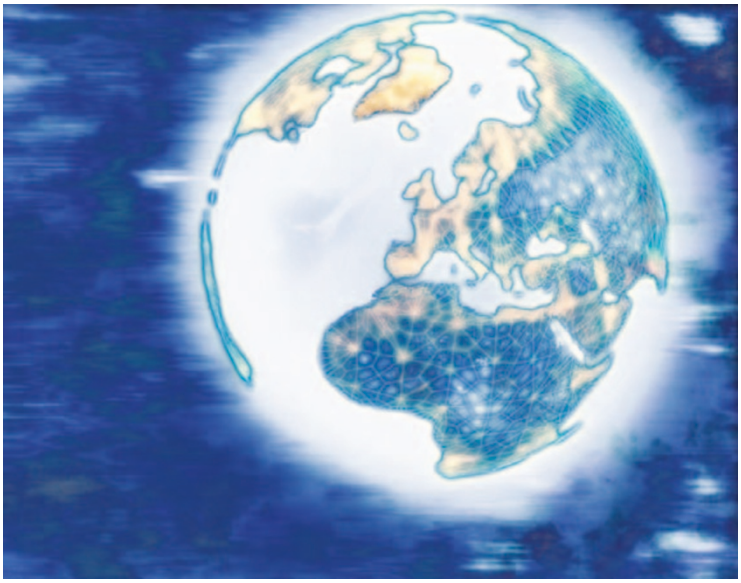
URLs
Alliance for Cellular Signaling: http://www.signaling-gateway.org

Cells are bombarded with numerous stimuli from the external environment, so, how does a cell process all of these inputs to produce appropriate outputs? A global analysis of crosstalk between signalling pathways now indicates that many external stimuli converge on a small number of interaction mechanisms that determine context-dependent signalling.

To experimentally assess the functional interactions between stimuli in one cell type, the Alliance for Cellular Signaling systematically measured output responses in macrophages. Both single-ligand screens with 22 receptor-specific ligands and double-ligand screens that used 231 combinations of 21 ligands produced results that were consistent with known signalling mechanisms and known interactions between signalling pathways.

However, the double-ligand screens also highlighted novel interactions between signalling pathways. For example, combining ligands that induce cyclic AMP production with those that induce Ca^{2+} mobilization caused increases in cAMP levels that were coupled to the synergistic inhibition of Ca^{2+} mobilization. Further analysis revealed that receptor-mediated elevations of intracellular Ca^{2+} levels lead to the potentiation of cAMP signalling. In turn, cAMP production, through the activation of protein kinase A, inhibits receptor-mediated Ca^{2+} mobilization.



To examine the total crosstalk between signalling pathways, the authors assessed the non-additive interactions for all of the 231 double combinations. Although many non-additive interactions were evident, the ligand pairs fell into a modest number of clusters (~40) on the basis of their pattern of non-additivity. These observations indicate that signalling pathways converge onto a small set of interaction mechanisms, which result in a limited number of unique cytokine regulatory programmes.

The authors propose that the topology of the signalling network in macrophages is composed of units that represent the core transduction machinery downstream of specific receptor classes. This machinery is linked by a limited set of interaction agents, the number and promiscuity of which determine the cellular response. The availability of an open-access data set of ligand responses, and of the interactions between them in different cell types, will provide a valuable tool for the signalling community.

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