The Ras/Raf/Mek/Erk Signaling Pathway - Attention to Details

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Cancer is caused by aberrant signaling in cells. Often mutations in important signaling pathways lead to faulty transmission of signals and cause cells to divide uncontrolled. The Ras/Raf/Mek/Erk pathway is one of the important pathways for the cell to relay signals from the plasma membrane to the nucleus and cytosolic targets. It is also frequently involved in the development of cancer.

Through years of research an extensive amount of data and knowledge about this pathway has been obtained, but we still find that key elements of our understanding are missing. To address this problem, we assembled a Boolean model of the pathway, to be able to simulate its behavior without making assumptions about rates and concentrations. During the assembly of the model we found a lack of data on short timescales, from the moment of stimulation of the pathway to about 30 minutes. We therefore performed an experiment with nine cell lines and four input stimuli to observe the behavior of phosphorylated Mek and Erk in this timespan. The data showed a marked difference between cell lines carrying a NRasQ61R mutation and those with a NRasQ61L mutation. Using our Boolean Model of the pathway, we propose a possible explanation for the observed behavior. The NRasQ61 site is known to play a role in the binding of GAP and the deactivation of NRas. Analogous to scaffold binding in kinases, the binding site for GAP could be shielded by a scaffold to protect it from premature deactivation. The Q61 residue could therefore play a role in binding the scaffold. The mutations would then affect not only the binding of GAP to NRas, but also the recruitment and binding of a possible scaffold protein.