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Title: The complexities and versatility of the RAS-to-ERK signalling system in normal and cancer cells

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Abstract: The intricate dynamic control and plasticity of RAS to ERK mitogenic, survival and apoptotic signalling has mystified researches for more than 30 years. Therapeutics targeting the oncogenic aberrations within this pathway often yield unsatisfactory, even undesired results, as in the case of paradoxical ERK activation in response to RAF inhibition. A direct approach of inhibiting single oncogenic proteins misses the dynamic network context governing the network signal processing. In this review, we discuss the signalling behaviour of RAS and RAF proteins in normal and in cancer cells, and the emerging systems-level properties of the RAS-to-ERK signalling network. We argue that to understand the dynamic complexities of this control system, mathematical models including mechanistic detail are required. Looking into the future, these dynamic models will build the foundation upon which more effective, rational approaches to cancer therapy will be developed.

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