Regulation of Raf kinase as predictor for therapeutic effects

The Raf kinase was discovered 30 years ago as a retroviral oncogen. It is activated in several human cancers and a major target of recent drug therapy. However, the Raf kinase can also induce differentiation instead of proliferation, depending on the cell-type and growth factor stimuli. We described a cross-talk between the Raf-kinase and the PI3Kinase pathways which influences the cellular responses. Thus, in cells where the Raf kinase is normally inducing differentiation, anti-cancer drugs may induce proliferation and cause an undesired opposite effect. This has been observed repeatedly in patients treated with one of the novel drugs against the Raf kinase. We also described previously two negative feedback loops inducing upstream signalling from Raf-MEK to the EGF receptor. Again, inhibition of this loop by drugs against Raf may induce the opposite effect. This was indeed observed in patients and therefore recently a dual therapy was applied in order to compensate for the loss of the negative feedback, with some therapeutic success. Considering the unexpected counterintuitive effects of Raf kinase inhibitors and novel therapeutics it is worth discussing the known regulatory mechanisms we have described, and avoid side-effects.

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