PS9 Invited

The roles of B-RAF and C-RAF in human cancer

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The protein kinase B-RAF is mutated in 30–70% of human melanomas and also in a range of other cancers. Over 50 different mutations have been described B-RAF in cancer, but the most common is a glutamic acid for valine substitution at position 600 (V600E). V600EB-RAF is activated 500 fold compared to wild-type B-RAF and it stimulates constitutive ERK and NFkB signalling in cancer cells, where it stimulates proliferation and survival. Structural studies reveal how the mutations in B-RAF in cancer activate the kinase and are also aiding the development of new anti-cancer drugs that target oncogenic B-RAF. In addition, we find drugs such as 17-AAG that inhibit the activity of the protein chaperone HSP90 target mutant forms of B-RAF, establishing that B-RAF is a client protein of this protein-folding complex. Some of these activities of V600EB-RAF in melanocytes are mediated through its ability to suppress expression of the transcription factor MITF, a key regulator of melanocyte differentiation. MITF is regulated by B-RAF through both protein stability and transcriptional mechanisms and these studies provide valuable insight into the mechanisms underlying the progression of melanoma. We are also developing mouse models of melanoma that express an inducible form of mutant B-RAF. Finally, a small number of mutant forms of B-RAF that occur in human cancer are inactive. However, they still signal to ERK because they activate the B-RAF related protein C-RAF. Although C-RAF appears to be less important than that of B-RAF in human cancer, in those rare cancers that express the inactive mutant forms of B-RAF, C-RAF does appear to play an essential role.