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Architecture of autoinhibited and active BRAF–MEK1–14-3-3 complexes

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ABSTRACT: RAF family kinases are RAS-activated switches that initiate signalling through the MAP kinase cascade to control cellular proliferation, differentiation and survival^{1,2,3}. RAF activity is tightly regulated and inappropriate activation is a frequent cause of cancer^{4,5,6}; however, the structural basis for RAF regulation is poorly understood at present. Here we use cryo-electron microscopy to determine autoinhibited and active-state structures of full-length BRAF in complexes with MEK1 and a 14-3-3 dimer. The reconstruction reveals an inactive BRAF–MEK1 complex restrained in a cradle formed by the 14-3-3 dimer, which binds the phosphorylated S365 and S729 sites that flank the BRAF kinase domain. The BRAF cysteine-rich domain occupies a central position that stabilizes this assembly, but the adjacent RAS-binding domain is poorly ordered and peripheral. The 14-3-3 cradle maintains autoinhibition by sequestering the membrane-binding cysteine-rich domain and blocking dimerization of the BRAF kinase domain. In the active state, these inhibitory interactions are released and a single 14-3-3 dimer rearranges to bridge the C-terminal pS729 binding sites of two BRAFs, which drives the formation of an active, back-to-back BRAF dimer. Our structural snapshots provide a foundation for understanding normal RAF regulation and its mutational disruption in cancer and developmental syndromes.

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