A-RAF, B-RAF, and C-RAF are a family of three protein-serine/threonine kinases that participate in the RAS-RAF-MEK-ERK signal transduction cascade. This cascade participates in the regulation of a large variety of processes including apoptosis, cell cycle progression, differentiation, proliferation, and transformation to the cancerous state. RAS mutations occur in 15–30% of all human cancers, and B-RAF mutations occur in 30–60% of melanomas, 30–50% of thyroid cancers, and 5–20% of colorectal cancers. Activation of the RAF kinases requires their interaction with RAS-GTP along with dephosphorylation and also phosphorylation by SRC family protein-tyrosine kinases and other protein-serine/threonine kinases. The formation of unique side-to-side RAF dimers is required for full kinase activity. RAF kinase inhibitors are effective in blocking MEK1/2 and ERK1/2 activation in cells containing the oncogenic B-RAF Val600Glu activating mutation. RAF kinase inhibitors lead to the paradoxical increase in RAF kinase activity in cells containing wild-type B-RAF and wild-type or activated mutant RAS. C-RAF plays a key role in this paradoxical increase in downstream MEK-ERK activation.

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the four RAS components can interact with each of the six RAF components, the total number of interactions between these two groups is $4 \times 6 = 24$ (Fig. 1). Assuming that each of the six RAF components can interact with each of the two MEK components, the total number of interactions between these two groups is $6 \times 2 = 12$. Both of the MEK components can phosphorylate and activate ERK1 and ERK2; the total number of interactions between MEK1/2 and ERK1/2 is $2 \times 2 = 4$. The total number of pathways from the four RAS components to the two ERK components is $24 \times 12 \times 4 = 1152$. If not all of the assumed interactions occur, this would decrease the number of combinations. However, the two isoforms resulting from alternative pre-mRNA splicing of CRAF potentially increases the number of pathways. Moreover, a variable number of adapter/scaffold proteins participate in the RAS-RAF-MEK-ERK interactions and including the adapter/scaffold interactions increases the number of pathways from RAS to ERK. The MAPK cascade is not a single linear pathway; rather, it is a highly branched pathway.

### 3. RAF kinase structures

Each of the RAF kinases shares three conserved regions (CR): CR1, CR2, and CR3 (Fig. 2) [3]. CR1 is composed of a RAS-binding domain (RBD) and a cysteine-rich domain (CRD), which can bind two zinc ions. CR1 interacts with RAS and with membrane phospholipids. CR2 is a serine/threonine-rich domain. It contains a site, when phosphorylated, that can bind to 14-3-3, a regulatory protein. Binding of 14-3-3 to this phosphorylated serine is inhibitory. CR3 is the protein kinase fold, which is located near the C-terminus. A stimulatory 14-3-3-binding site occurs after the kinase domain.

The RAF protein kinase domain has the characteristic small N-terminal lobe and large C-terminal lobe found in all protein kinases (Fig. 3). The small lobe has a predominantly antiparallel $\beta$-sheet structure and anchors and orients ATP. It contains a glycine-rich ATP-phosphate-binding loop, sometimes called the P-loop. The large lobe is mainly $\alpha$-helical. The large lobe binds MEK1/2, the protein substrates. The catalytic site lies in the cleft between the small and large lobes. In Fig. 3, this cleft is occupied by sorafenib, an ATP-competitive inhibitor, which has been approved by the US Food and Drug Administration for the treatment of advanced kidney and liver cancers [5].

The two lobes of protein kinases move relative to each other and can open or close the cleft. The open form allows access of ATP and release of ADP from the active site. The closed form brings and can open or close the cleft. The open form allows access of large lobe is mainly a C-helix. The large lobe binds MEK1/2, the protein substrates. The catalytic site lies in the cleft between the small and large lobes. In Fig. 3, this cleft is occupied by sorafenib, an ATP-competitive inhibitor, which has been approved by the US Food and Drug Administration for the treatment of advanced kidney and liver cancers [5].

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In the large lobe, the activation segment adjusts to make or break part of the ATP-binding site. The activation segment of all protein kinases begins with a DFG (Asp/Phe/Gly) amino acid sequence. In the inactive conformation, the phenylalanine side chain occupies the ATP-binding pocket, and the aspartate side chain faces away from the active site [6]. This is called the DFG-Asp out conformation. In the active conformation, the phenylalanine side chain is rotated out of the ATP-binding pocket, and the aspartate side chain faces into the ATP-binding pocket and coordinates Mg$^{2+}$. This is called the DFG-Asp in conformation. The activation segment of most protein kinases contains one or more phosphorylation sites. These sites are usually phosphorylated by reactions catalyzed by members of the same protein kinase family, but they may be phosphorylated by other protein kinases. For example, the RAF kinases activate MEK1/2 by catalyzing the phosphorylation of two serine residues that occur within the activation segment.

A gatekeeper residue in many protein kinases separates the adenine-binding site from an adjacent hydrophobic pocket. Some kinase inhibitors bind to the adenine-binding site and extend into the hydrophobic pocket. Mutation of a small gatekeeper residue
(threonine) to a larger one (methionine) can prevent the binding of kinase inhibitory drugs. This is one mechanism for acquiring resistance to drugs in the clinic, and this strategy can be used experimentally to create enzymes that do not bind to a given drug.

Hanks and colleagues identified 12 subdomains with conserved amino acid residue signatures that constitute the catalytic core of protein kinases [7]. Of these, the following three amino acids, which define a K/D/D (Lys/Asp/Asp) motif, illustrate the catalytic properties of B-RAF. An invariant lysine (Lys578 in B-RAF) forms salt bridges with the $\gamma$-phosphate of ATP (Fig. 4). Asp576, which is a base occurring in the catalytic loop, orients the seryl or threonyl group of the substrate protein and abstracts the proton from the $–OH$ group thereby facilitating the nucleophilic attack of oxygen on the $\gamma$-phosphorus atom of MgATP. Asp594 is the first residue of the activation segment. The activation segment of nearly all protein kinases begins with DFG and ends with APE (Ala/Pro/Glu). However, the activation segment of A-RAF ends with AAE (Ala/Ala/Glu). Asp594 binds Mg$^{2+}$. This in turn coordinates the $\beta$– and $\gamma$- phosphates of ATP (Fig. 4). Functionally important RAF kinase residues are listed in Table 1.

### 4. Regulation of RAF kinase activity

The physiological regulation of RAF kinases is intricate and involves several steps including protein–protein interactions, phosphorylation, dephosphorylation, and conformational changes [3]. Most RAF kinase protein occurs in the cytosol where the enzymes are in their dormant state. Under non-stimulatory conditions, a serine occurring within CR2 and another near the C-terminus are phosphorylated and are bound to 14-3-3 (Fig. 2). RAS-GTP interacts with the Ser582Ala mutant is not as strongly stimulated by the activated Ras Gly12Val mutant co-expressed with the Src kinase Lck in monkey kidney COS-7 cells, suggesting that 14–3–3 participates in A-RAF activation. They also found that basal and inducible A-RAF kinase activity is considerably increased in the Ser214Ala mutant when compared with the wild-type enzyme. Both results support a role for 14–3–3 binding in the regulation of A-RAF kinase activity. Baljuls et al. found that Ser432, Thr452, and Thr455 are phosphorylated [12]. They showed that Ser432, which occurs in the catalytic loop, is required for kinase activity and for MEK1/2 binding. They reported that single mutations at serines 257, 262 and 264 in the isoform specific hinge (IH) region (Fig. 2) strongly impair A-RAF kinase activity following epidermal growth factor stimulation of COS-7 cells. Phosphorylation of residues within the IH segment is stimulatory.

### 5. C-RAF regulation

In C-RAF, the most prominent basal phosphorylation sites are Ser259 and Ser621 [9]. Phosphorylation of these residues is necessary for binding the 14–3–3 proteins. Phosphorylation at Ser259 suppresses C-RAF kinase activity. Zhu and colleagues reported that phosphorylation of Ser471, which occurs in the catalytic loop, is required for C-RAF activity [10]. They demonstrated that this modification is required for the interaction of C-RAF with its protein substrates. The RAF enzymes have restricted substrate specificity and the only commonly agreed upon substrates for all three kinases are MEK1 and MEK2.

C-RAF contains two phosphorylation sites within the activation segment (Thr491, Ser494), and phosphorylation of these sites is stimulatory [11]. Treatment of cells with growth factors induces phosphorylation of C-RAF at multiple sites within the N-terminal half of the protein. Phosphorylation of Ser338, and Tyr341, which occur in the N-region, or negatively-charged regulatory region (Fig. 2), is stimulatory. Tyr341 phosphorylation is catalyzed by SRC family kinases. Dougherty and co-workers reported that serine residues 29, 43, 289, 296, 301, and 642 are ERK-catalyzed phosphorylation sites associated with feedback inhibition [9].

### 6. A-RAF regulation

Baljuls and colleagues identified 35 phosphorylation sites in human A-RAF by mass spectrometry [12]. This corresponds to more than 34 billion combinations of phosphorylation states (Fig. S1). They identified the inferred 14–3–3 binding sites in A-RAF (Ser214 and Ser582) as phosphorylation sites. They showed that the Ser582Ala mutant is not as strongly stimulated by the activated Ras Gly12Val mutant co-expressed with the Src kinase Lck in monkey kidney COS-7 cells, suggesting that 14–3–3 participates in A-RAF activation. They also found that basal and inducible A-RAF kinase activity is considerably increased in the Ser214Ala mutant when compared with the wild-type enzyme. Both results support a role for 14–3–3 binding in the regulation of A-RAF kinase activity. Baljuls et al. found that Ser432, Thr452, and Thr455 are phosphorylated [12]. They showed that Ser432, which occurs in the catalytic loop, is required for kinase activity and for MEK1/2 binding. They reported that single mutations at serines 257, 262 and 264 in the isoform specific hinge (IH) region (Fig. 2) strongly impair A-RAF kinase activity following epidermal growth factor stimulation of COS-7 cells. Phosphorylation of residues within the IH segment is stimulatory.

### 7. B-RAF regulation

Phosphorylation of Ser365 in the CR2 region and Ser729 near the C-terminus is required for 14–3–3 binding. Phosphorylation of Thr599 and Ser602, which occur within the activation segment, is essential for B-RAF activation [3]. Zhu and colleagues found that phosphoserine 579, which occurs in the catalytic loop, is essential for B-RAF kinase activity [10]. Although not tested directly, this is most likely related to the importance of this residue in binding its substrates (MEK1/2). A-RAF and C-RAF require protein-kinase-catalyzed phosphorylation of residues in the N-region for activation. The N-region of B-RAF contains Asp448 and Asp449, which bear negative charges. Moreover, Ser446 is constitutively phosphorylated. The N-region of B-RAF thus contains negative charges and does not require additional enzyme-catalyzed modifications to become negatively charged during activation. The basal activity of B-RAF is greater than that of C-RAF, which is greater than that of A-RAF. Ritt and colleagues reported that Ser151, Thr401, Ser750, and Thr753 are ERK-catalyzed phosphorylation sites associated with feedback inhibition [13]. Except for the Erk phosphorylation sites, the protein kinases that catalyze the phosphorylation of most of the A-, B- and C-RAF serine/threonine sites are unknown.

B-RAF mutants occur in a variety of cancers while mutants of the other two RAF enzymes in cancers are very rare. The majority of B-RAF mutations occur in the activation segment or in the
glycine-rich loop [14]. These mutations disrupt the inactive state to favor the active state. A Val600Glu mutation accounts for >90% of all of the 65 or more known B-RAF mutations. This mutation occurs within the activation segment where the introduction of negative charges favors the formation of an active conformation. The introduction of glutamate into the activation segment of C-RAF fails to produce an activated enzyme most likely owing to the need for a negatively charged N-region for activity.

8. RAF dimerization is necessary for kinase activity

RAF kinases form both homodimers and heterodimers [15]. Rushworth and colleagues demonstrated that Ser621 and residues occurring within the αC helix of C-RAF participate in dimer formation [15]. They reported that B-RAF–C-RAF heterodimers are more active that either homodimer. Phosphorylation of B-RAF at Thr753 and the catalytic domain of human B-RAF forms homodimers. Arg509 of B-RAF contains only one RAF kinase, a C helix, an important determinant of kinase activity and dimer formation is necessary for the expression of RAF kinase activity. Activation occurs even when one monomer is kinase-dead.

9. The RAF inhibitor paradox

RAF kinase inhibitors effectively block MEK and ERK phosphorylation and activation in cell lines and xenografts that harbor activated mutant B-RAF (V600E) [17–19]. Heidorn and colleagues found, however, that the B-RAF specific inhibitor 885-A produces an unexpected increase in ERK phosphorylation in four human melanoma cell lines bearing activated NRAS mutations. How can a RAF kinase inhibitor lead to the paradoxical increase in RAF kinase activity and ERK phosphorylation? Two additional studies noted below address this issue, and the common finding is that the binding of inhibitors to RAF kinases promotes RAS-dependent C-RAF homo- or heterodimerization and C-RAF activation.

Heidorn et al. showed that depletion of NRAS and C-RAF by RNA interference blocks the ability of 885-A to activate ERK, indicating that RAS and C-RAF participate in the paradoxical response [17]. They reported that 885-A binding to B-RAF or mutation to a kinase-dead B-RAF drives their binding to C-RAF in COS-7 cells. The introduction of a gatekeeper mutation in B-RAF abolishes the ability of B-RAF inhibitors to induce the binding of B-RAF to C-RAF. Inhibitor binding to B-RAF in the presence of activated RAS induces B-RAF binding to C-RAF leading to C-RAF activation and increased downstream ERK phosphorylation and activation.

In a second study, Poulikakos et al. reported that six ATP-competitive RAF inhibitors induce ERK activation in cells with activated RAS and wild-type B-RAF but inhibit signaling in activated mutant B-RAF (V600E) cells [18]. The RAF inhibitor PLX4032 induces ERK signaling in human SKBR3 breast adenocarcinoma cells, in which RAS activation is HER2 dependent. The HER2 inhibitor lapatinib abolishes basal and PLX4032-induced ERK signaling. The results indicate that RAS is required for MEK-ERK activation by RAF inhibitors.

B-RAF and C-RAF form homo- and heterodimers following RAS activation [18]. PLX4032 and PLX4720, RAF kinase inhibitors, induce the phosphorylation of MEK and ERK in wild-type and Braf<sup>−/−</sup> mouse embryonic fibroblasts. The response is diminished in Craf<sup>−/−</sup> fibroblasts, arguing for the importance of C-RAF in paradoxical MEK-ERK activation.

In transformed human embryonic kidney 293H cells expressing the catalytic domain of C-RAF (catC), PLX4032/PLX4720 induce MEK and ERK phosphorylation [18]. In contrast, ERK signaling is not induced by PLX4032/PLX4720 in cells expressing catC bearing

### Table 1

<table>
<thead>
<tr>
<th>Residue</th>
<th>A-RAF</th>
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<th>C-RAF</th>
</tr>
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<tr>
<td>CRRD</td>
<td>19–91</td>
<td>155–227</td>
<td>56–131</td>
</tr>
<tr>
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<td>98–144</td>
<td>234–280</td>
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<tr>
<td>CR1</td>
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<td>150–290</td>
<td>51–194</td>
</tr>
<tr>
<td>CR2</td>
<td>209–224</td>
<td>360–375</td>
<td>294–269</td>
</tr>
<tr>
<td>CR3, protein kinase domain</td>
<td>310–570</td>
<td>451–717</td>
<td>349–609</td>
</tr>
<tr>
<td>Glycine-rich loop</td>
<td>316–324</td>
<td>463–471</td>
<td>355–363</td>
</tr>
<tr>
<td>14-3-3 binding sites</td>
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<td>S365, S729</td>
<td>S259, S621</td>
</tr>
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<td>Gatekeeper residue</td>
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<td>T421</td>
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<td>427–429</td>
<td>574–576</td>
<td>466–468</td>
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<tr>
<td>K of K/D/D</td>
<td>431</td>
<td>578</td>
<td>470</td>
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<td>DFG</td>
<td>447–449</td>
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<td>T599, S602</td>
<td>T491, S494</td>
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<td>APE, 621–623</td>
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<tr>
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<sup>a</sup> Molecular weight of the non-phosphorylated enzyme.
a gatekeeper mutation (Thr421Met), which prevents drug binding. Poulikakos et al. found that sorafenib inhibits catC (Thr421Met) and induces ERK signaling in cells expressing catC (Thr421Met), demonstrating that this mutant is capable of inhibitor-induced MEK-ERK activation. This finding suggests that the binding of an ATP-competitive inhibitor to C-RAF is sufficient for the induction of MEK-ERK signaling. These workers also showed that a mutation that blocks C-RAF homodimer formation prevents transactivation and downstream MEK-ERK activation.

In a third study, Hatzivassiliou and colleagues reported that RAF inhibitor treatment results in the paradoxical induction of phospho-MEK and phospho-ERK levels in the wild-type RAS/RAF human melanoma (MeWo) or activated mutant KRAS non-small cell lung cancer (H2122) cells versus their sustained inhibition in B-RAF(V600E) human melanoma A375 cells [19]. They showed that knockdown of C-RAF, but not B-RAF, in human colorectal carcinoma HCT116 (mutant KRAS) cells reverses the phospho-MEK induction observed after RAF inhibitor treatment, indicating that C-RAF has a major role in signaling to MEK, a result that is in agreement with the above two studies. Both B-RAF and C-RAF kinase activities increase in a concentration-dependent manner after RAF inhibitor GDC-0879 treatment in non-B-RAF(V600E) lines. Activation of A-RAF is observed after GDC-0879 treatment, and dual A-RAF and C-RAF knockdown is synergistic in decreasing inhibitor-induced phospho-MEK levels in activated mutant KRAS HCT116 cells. These workers showed that GDC-0879 induces B–C and A–B heterodimer formation together with the induction of A-, B- and C-RAF kinase activities. After transfection and expression of a dominant-negative KRAS Ser17Asn mutant, the induction of phospho-MEK is significantly impaired in non-B-RAF(V600E) lines, indicating that wild-type or activated mutant RAS is required for paradoxical activation.

Hatzivassiliou and colleagues showed that RAF inhibitors induce C-RAF homodimer formation [19]. These investigators showed by X-ray crystallography that C-RAF kinase forms side-to-side dimers as observed with B-RAF [4]. They generated C-RAF and B-RAF dimer interface mutants that either constitutively heterodimerize (C-RAF [Glu478Lys] and B-RAF [Glu586Lys]) or are defective in dimerization (C-RAF [Arg401His] and B-RAF [Arg509His]). Co-transfection of C-RAF [Glu478Lys] and B-RAF [Glu586Lys] in activated mutant KRAS HCT116 cells results in an increase of basal C-RAF kinase activity compared to wild-type controls. No further induction is observed after RAF inhibitor treatment, confirming that dimerization is the main driver for the inhibitor effects on C-RAF kinase activity. In contrast, co-transfection of C-RAF [Arg401His] and B-RAF [Arg-509His] leads to decreased levels of basal C-RAF activity and a significant impairment of C-RAF activation by RAF inhibitors.

These studies indicate that the binding of an inhibitor to C-RAF leads to the formation of a C-RAF homodimer and C-RAF activation resulting in downstream MEK-ERK activation. Another possible, but not mutually exclusive, mechanism is that binding of an inhibitor to B-RAF leads to the formation of a B-RAF–C-RAF heterodimer and C-RAF activation. That RAF kinase-induced paradoxical activation occurs in BrafT17 mouse embryonic fibroblasts does not rule out the possibility that B-RAF–C-RAF heterodimers play a role in paradoxical activation. The experiments of Hatzivassiliou and colleagues suggest that A-RAF may also participate in the paradoxical response.

10. Epilogue

RAF kinases are attractive cancer drug targets. Pre-clinical studies with cell lines and tumor xenographs bearing B-RAF(V600E) mutations indicate that RAF kinase inhibitors are effective in decreasing cell proliferation. PLX4032, which has higher affinity for BRAF(V600E) than wild-type B-RAF, inhibits cancer progression in several animal models. The compound has demonstrated efficacy in Phase I clinical trials in the treatment of melanoma patients [20]. Sorafenib has a lower affinity for B-RAF than C-RAF and is ineffective as monotherapy in the treatment of melanoma. RAF kinase inhibitor treatment of cancers with wild-type or activated mutant RAS co-expressed with wild-type B-RAF may be deleterious owing to up-regulation of RAF kinase signaling. Deciphering the mechanisms of RAS-RAF-MEK-ERK signaling continues to be an important and challenging task.

Appendix A. Supplementary data


References


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