20 years of Raf kinase

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Abstract

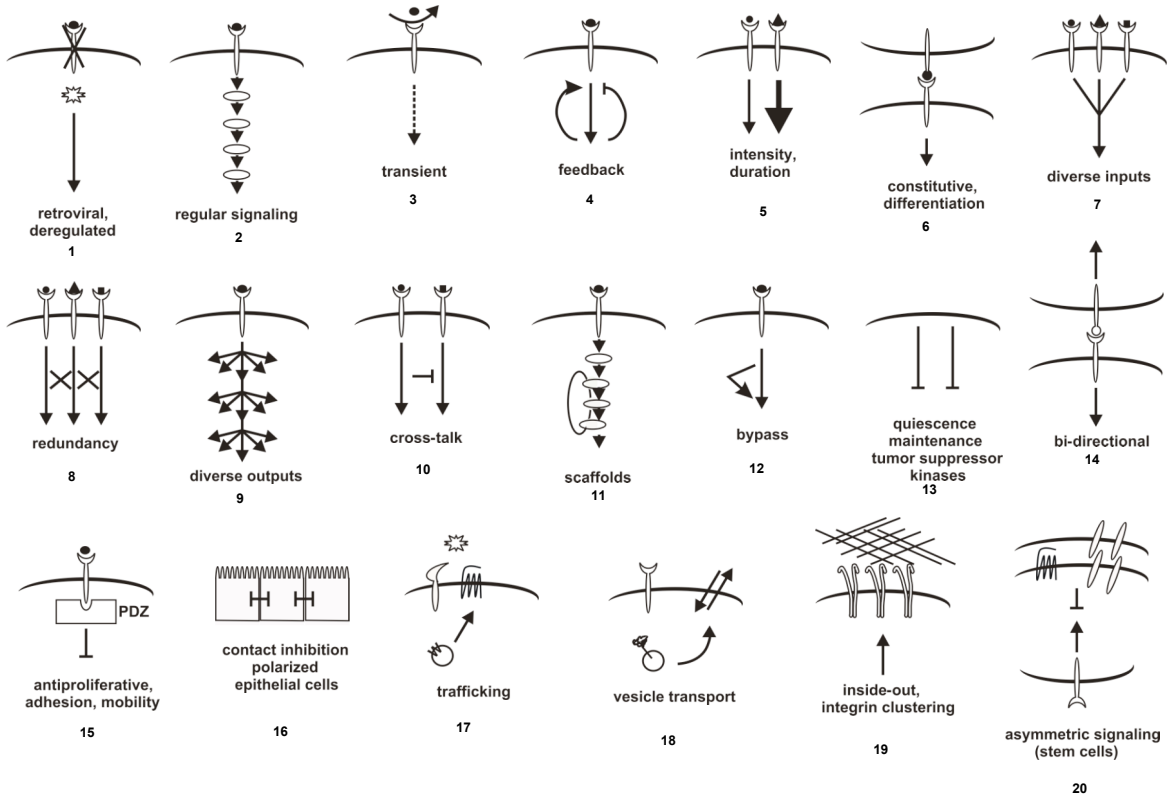
The Raf kinase is an important signal transducer. It has isoforms, homologues, and structural features and biological properties, characteristic of many kinases. Based on known Raf-mediated signal transduction pathways one can draw simple stick models about signaling. These comprise positive or negative feedbacks, cross-talk, signal integration, bidirectional signaling, lateral signaling, transient or constituent signaling, inside-out, outside-in signaling, oscillations, etc. Electrical circuits can help to simplify apparently complex situations. 20+ knowledge-based models will be presented and the question raised about prediction of further unknown ones. Some suggestions will be made. A mathematical description is also presented.

The 20 first models are based on our and others work and are retrospective. Some other ones are added on recent results from us or others.

How about prospective models?

Is an oscillator model meaningful or something to look for?

Draw and test your own model!



1. Signaling through v-onc from within, v-Raf is less active than c-Raf, unlike v/c-Src.

2. Ras-Raf-MEK-ERK signaling with growth factor stimulation of RTK.

3. Transient stimulation by soluble growth factor.

4. Positive or negative feedback (ERK and Ras).

5. Ligand-RTK interaction varies in duration and intensity of signal (EGF vs NGF).

6. Membrane-associated ligand and receptor interaction leading to constitutive stimulation and differentiation.

7. Diverse inputs are integrated , e.g. Ras and Src activate Raf.

8. Redundancy of signals reduce the risk of defects.

9. Diverse signalling from Ras but not from Raf.

10. Cross-talk for modulation of signaling, Akt-Raf cross-talk can lead to proliferation or differentiation, depending on relative signal intensities. Strong Raf signaling can correlate with senescence or growth inhibition.

11.Scaffold molecules help to organize and modulate signaling.

12.There can be a bypass, e.g. RIP2 by-passes MEK.

13.Active signaling occurs through quiescence kinases such as Bcr or GSK3 for maintenance of the non-proliferative state of the cell, their inactivation contributes to cell proliferation. Thus they are functionally tumor-suppressor-like molecules. (Bcr e.g. phosphorylates AF-6 which then inactivates the R-R-M-E pathway, this is reversed by growth factor stimulation).

14.Bidirectional signaling is a characteristic of pathfinding of neurons or angiogenesis (e.g. Eph receptor- Ephrin interaction).

15.PDZ-domain proteins negatively regulate signaling or integrate diverse signals for differentiation (e.g.Ina D). They affect adhesion or cellular mobility. Src is negatively regulated by a PDZ protein.

16.PDZ-domain proteins are essential at cell-cell junctions, e.g. of epithelial cells. They contribute to contact inhibition, cell polarization or maintenance of epithelial cell layers. In individual cells directionality or invasiveness are regulated through PDZ domains.

17.HIV-infection leads to signaling through receptors, CD4 and GPCR, trafficking is affected.

18. A WD-repeat propeller protein linked to vesicles via its FIVE-domain transports kinases, Akt and PKC, and substrates for glucose metabolism of adipocytes.

19.Inside-out signaling can occur with integrins and B-Raf.

20.Asymmetrical signalling allows stem cells to stay in a niche with one part of the cell via cadherins and to proliferate at the exposed side after growth-factor stimulation.