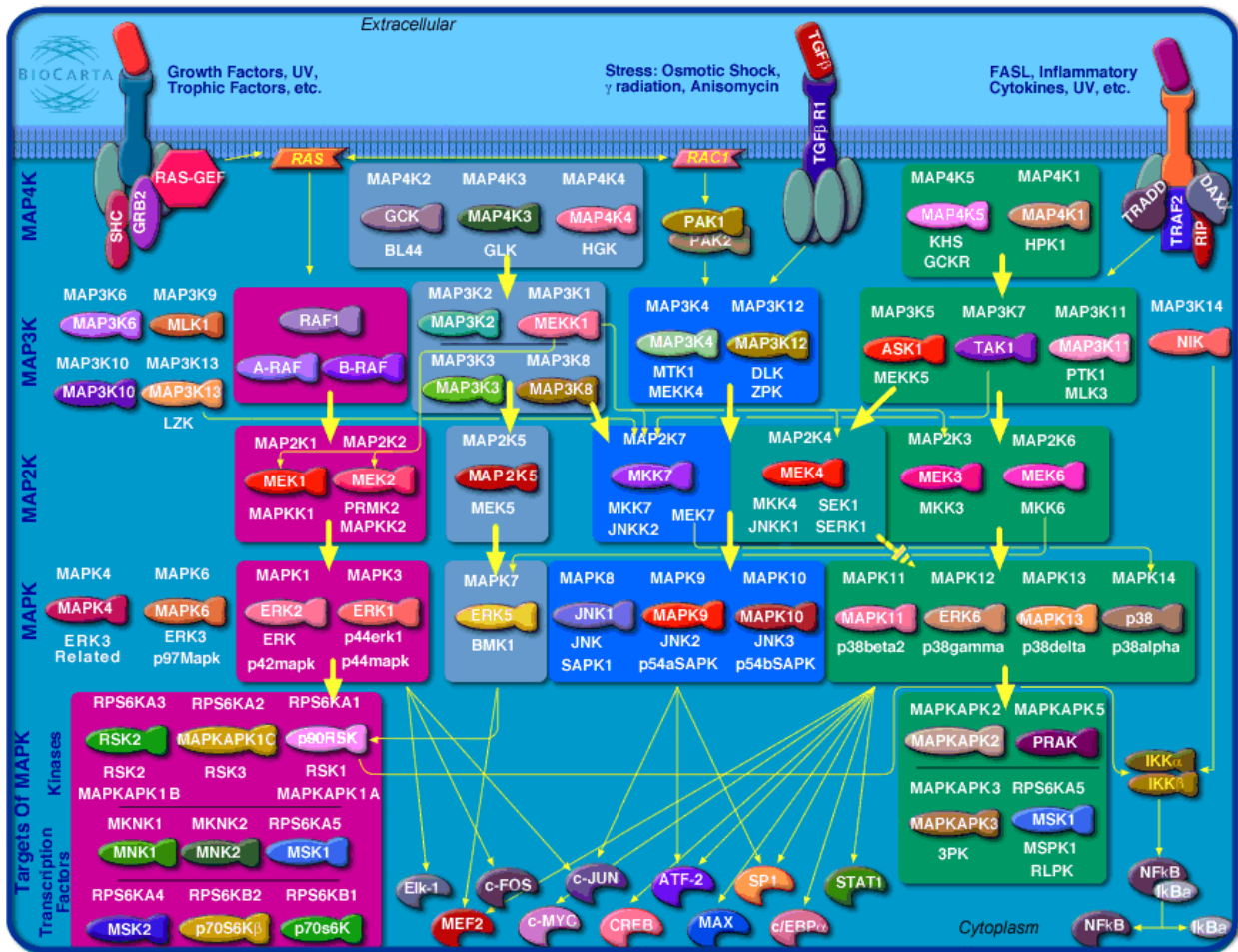


Map38



The ever evolving mitogen-activated protein kinase (MAP kinase) pathways consist of four major groupings and numerous related proteins which constitute interrelated signal transduction cascades activated by stimuli such as growth factors, stress, cytokines and inflammation. The four major groupings are the Erk (red), JNK or SAPK (blue), p38 (green) and the Big MAPK or ERK5 (light blue) cascades. Signals from cell surface receptors such as GPCRs and growth factor receptors are transduced, directly or via small G proteins such as ras and rac, to multiple tiers of protein kinases that amplify these signals and/or regulate each other. The diagram is organized to illustrate the cascades by the background colors and also the tiers of kinases as indicated down the left hand side and separated by the horizontal dashed lines. In some cascades the first activation tier involves the MAPKKKKs, MAP kinase kinase kinase kinases or MAP4K proteins. The next tier are the serine/threonine MAPKKKs, MAP kinase kinase kinase or MAP3Ks such as RAF, TAK, ASK, and MEKK1. This level has the greatest amount of cross-communication currently known. The serine/threonine/tyrosine MAPKKs, MAP Kinase kinases or MAP2Ks, such as the MKK and MEK kinases, are one step up from the MAP kinase cascade, phosphorylating and activating these

kinases. The focal tier, the MAPKs or MAP kinases includes JNK1, p38, and ERKs, and are the kinases that give each cascade its name. The endpoints of these cascades, shown in the bottom tier, includes the MAPK activated protein kinases (MAPKAPK) and some of the numerous transcription factors that regulate genes involved in apoptosis, inflammation, cell growth and differentiation.

NOTES:- The shared color and the bold arrows show the major flow of each cascade.

- The smaller arrows indicate cross communication between cascades. In many cases this is restricted to certain cell types or requires additional factors.
- Kinases that have been identified as MAP kinases based on sequence or structural homologies but have not yet been assigned to a cascade have been placed outside the grouping backgrounds.
- The PAKs (p21 associated kinases) are not MAPKs but participate in the transduction to the JNK cascade are included for this reason.)
- MEK4 appears to function in both the JNK and p38 cascades and so has a mixed color. MEK4 signal is much stronger in the JNK than the p38 cascade and so the bold arrow towards the JNK and the dashed arrow towards the p38 cascade indicate the relative strengths of signaling.
- For space and readability concerns not all interactions and stimuli are indicated and the scaffold and phosphatase proteins are not shown.