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Opinion

Classification of Mitogen Activated Protein Kinases (MAPK)

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INTRODUCTION

Mitogen is a chemical substance that encourages a cell to commence cell division by triggering mitosis. A mitogen is usually a form of protein. Mitogens act primarily by influencing a set of proteins which are involved in the restriction of progression through the cell cycle. Only the G_1 checkpoint is controlled most directly by mitogens.

MAP kinases are intermediates in signal transduction pathways which are initiated by many types of surface receptors. The targets of MAPK are located within many cellular compartments. MAPK provide a physical link in the signal transduction pathway from the cytoplasm to the nucleus. Each MAPK pathway contains a three tiered kinase cascade comprising a MAP kinase Kinase Kinase Kinase (MAPKKK) and a MAP Kinase Kinase (MAPKK) and the MAPK.

DESCRIPTION

In humans, there are atleast 11 members of the MAPK superfamily, which can be divided into 6 groups such as:

- Extracellular signal regulated protein kinases (ERK1 and ERK2).
- c-Jun N-terminal kinases (JNK1, JKN2, JNK3).
- p38s (p38α, p38β, p38γ, p38δ).
- ERK5.
- ERK3s (ERK3, p97, ERK4).
- ERK7s (ERK7, ERK8).

Each group of MAPK can be stimulated by a separate signal transduction pathway in response to different extracellular stimuli.

Extracellular signal regulated protein kinases

In certain cells their activation contributes to normal and aberrant growth and in other cells they promote cell survival or initiate differentiation in others. Their enzymatic activity is enhanced by dual phosphorylation on Thr and Tyr, by a group of dual-specificity protein kinases (MAPKK) represented by MEK1 and MEK2. ERK activity is terminated by dephosphorylation on either Thr or Tyr by a Ser/Thr or Tyr phosphatase. MEK1 and MEK2 are activated by phosphorylation mediated by MAPKKK that include A-Raf, B-Raf, C-Raf-1. The Raf group is activated by small G-protein Ras.

c-Jun N-terminal kinases

JNK was discovered by its ability to phosphorylate the N-terminal transactivating domain of the transcription factor c-Jun. Its activity was stimulated primarily by cellular stress. The kinase cascade is initiated by the Rho family of GTPases, Rac1 and Cdc42. MAPKKK include MEK1, MEK2, MEK3, MEK4, Apoptosis Stimulated Kinase 1 (ASK1) and Germinal Center Kinase (GCK). MAPKK comprises of MKK4 and MKK7. Substrates for JNK include transcription factors of c-Jun family as well as several other transcription factors.

p38s

These MAPKs are stimulated by environmental stresses, they are particularly sensitive to their stimulation by exposure of cells to endotoxins. They are activated by dual phosphorylation on Thr and Tyr by MKK3 and MKK6. The specific transcription factors regulated by these MAPKs include CAMP Responsive Element Binding Protein (CREB) and several others. In addition, these MAPKs can also trigger the activation of other serine-threonine kinases.

ERK5

It is also known as big mitogen activated protein kinase, being larger than any other known MAPK. It is selectively activated by MEK5 but not by MEK1 or MEK2. It can be activated by oxidative stress and can play a role in early gene expression triggered by EGF. This MAPK cooperates with the activated Raf or MEK, which act on ERK1 and ERk2, to promote neoplastic transformation. The physiological role of ERK5 is unclear.

ERK3s

The ERK3 subfamily of MAPKs is composed of two functional genes and several pseudogenes. Upstream activators of ERK3 are poorly defined and this kinase is not present in yeast or C.

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elegans. None of the currently known MEKs are able to phosphorylate and activate ERK3 and no physiological substrate of ERK3 has been found. ERK3 is localized constitutively to nucleus.

CONCLUSION

Since the ERK signalling pathway is involved in both physiological and pathological cell proliferation, it is natural that ERK1/2 inhibitors would represent a desirable class of antineoplastic agents. JNK kinases are implicated in the development of insulin resistance in obese individuals as well as neurotransmitter excitotoxicity after ischemic conditions. p38 was once believed to be a perfect target for anti-inflammatory drugs. Yet the failure of more than a dozen chemically different compounds in the clinical phase suggests that p38 kinases might be poor therapeutic targets in autoimmune diseases.