DOCUMENT SUMMARY

This 2000 review by Roger J. Davis provides a comprehensive overview of the **JNK** (c-Jun NH2-terminal kinase) signal transduction pathway, a critical component of the **MAP kinase (MAPK)** family. The paper details the molecular architecture of the JNK signaling cascade, including its activation by stress and cytokines, its regulation by scaffold proteins, and its crucial roles in cellular processes. It particularly focuses on JNK's function in regulating **AP-1** transcription activity, embryonic development, and its dual role in promoting both apoptosis (cell death) and cell survival depending on the context.

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- cheung_2000_research_report_histone_modification_epigenetics
- ramirez-weber_2000_research_report_cytonemes_cell_signaling **Supersedes:** N/A

FORMATTED CONTENT

Signal Transduction by the JNK Group of MAP Kinases

Introduction

Cells respond to changes in the physical and chemical properties of the environment. These changes include alterations in the amount of nutrients, growth factors, cytokines, and adhesion to the cell matrix. In addition, cells respond to physical stimulation mediated by osmolarity, heat, pH, redox, radiation, and mechanical stress. These physical and chemical cues control many aspects of cell function including migration, proliferation, differentiation, and death. Recent studies have established that **mitogen-activated protein kinases (MAPK)** play an important regulatory role.

In mammals, three major groups of MAPK have been identified. The **ERK** and **p38** groups of MAPK are related to enzymes found in budding yeast. The **c-Jun NH2-terminal kinases (JNK)**, also known as stress-activated MAP kinases (SAPK), represent a third group of MAPK that has been identified in mammals. JNK is activated by treatment of cells with cytokines (e.g., TNF and IL-1) and by exposure of cells to many forms of environmental stress (e.g., osmotic stress, redox stress, and radiation).

The purpose of this review is to summarize recent advances that have been made toward understanding the JNK signaling pathway. It is now known that JNK is required for embryonic morphogenesis and that this signaling pathway contributes to the regulation of cell proliferation and **apoptosis**.

JNK Regulates AP-1 Transcription Activity

Phosphorylation of **c-Jun** on the sites that are phosphorylated by JNK (Ser-63 and Ser-73) causes increased transcription activity. Interestingly, JNK also phosphorylates other **AP-1** proteins, including JunB, JunD, and ATF2. Substrate recognition by JNK requires a docking site to tether the kinase to the substrate.

> A critical role for JNK appears to be the regulation of **AP-1** transcription activity. This conclusion is supported by genetic analysis of Jun and JNK in *Drosophila* and by the analysis of AP-1 transcription activity in murine cells with targeted disruptions of genes that encode components of the JNK pathway.

The JNK Group of MAPK

The JNK protein kinases are encoded by three genes (**Jnk1**, **Jnk2**, and **Jnk3**). The *Jnk1* and *Jnk2* genes are expressed ubiquitously. In contrast, the *Jnk3* gene has a more limited pattern of expression and is largely restricted to brain, heart, and testis. These genes are alternatively spliced to create ten JNK isoforms.

The analysis of *Jnk* gene disruptions in mice confirms that there is extensive complementation between the *Jnk* genes and that there are also tissue-specific defects in signal transduction that may reflect the JNK isoform profile of individual tissues. Mice deficient of JNK1 or JNK2 appear to be morphologically normal. However, these mice are immunodeficient due to severe defects in T cell function.

JNK Is Activated by Two Dual-Specificity Protein Kinases

The JNK protein kinases are activated by phosphorylation on Thr and Tyr by **MKK4** (also known as SEK1) and **MKK7**. These protein kinases are expressed as a group of alternatively spliced isoforms.

- **MKK7** is primarily activated by cytokines (e.g., TNF and IL-1).
- **MKK4** is primarily activated by environmental stress.

Although MKK4 and MKK7 are dual specificity protein kinases and do phosphorylate JNK on both Thr and Tyr, MKK4 and MKK7 appear to preferentially phosphorylate JNK on Tyr and Thr, respectively. This difference in specificity suggests that MKK4 and MKK7 may cooperate to activate JNK under some circumstances.

The JNK Pathway Is Activated by a Large Group of MAPKKK

Several **MAPKKK** (MAPK Kinase Kinases) have been reported to activate the JNK signaling pathway. These include members of the **MEKK** group, the **mixed-lineage protein kinase (MLK)** group, the **ASK** group, **TAK1**, and **TPL2**. It is unclear which MAPKKK are relevant to specific physiological stimuli, likely due to functional redundancy and promiscuity of function observed in overexpression and in vitro assays.

Mechanism of MAPKKK Activation

Several lines of evidence indicate that **Rho family GTPases** mediate the activation of JNK by some stimuli. The activation of JNK by cytokine receptors appears to be mediated by the **TRAF** group of adaptor proteins. Activation of the TNF receptor leads to recruitment of **TRAF2**, which is required for JNK activation. It is likely that other adaptor proteins contribute to the activation of the JNK pathway.

Molecular Scaffold Proteins Assemble JNK Signaling Modules

Protein-protein interactions are thought to be critical for the normal function of the JNK signaling pathway. Indeed, signaling specificity may be mediated through the formation of protein complexes. **Scaffold proteins** for the JNK group of MAPK have been identified. These include the **JNK interacting protein (JIP)** group of putative scaffolds.

The **JIP1** and **JIP2** proteins are closely related proteins that bind to JNK, MKK7, and mixed-lineage protein kinases. The **JIP3** protein is structurally unrelated to JIP1 and JIP2 but also appears to function as a scaffold protein for the JNK signaling pathway.

> The JIP proteins have been proposed to act as molecular scaffolds that organize the JNK signal transduction pathway in response to specific stimuli. The assembly of the JNK module by a scaffold protein may lead to the efficient activation of JNK within a restricted region of the cell by a particular stimulus.

The JNK-Dependent Apoptotic Signaling Pathway

The JNK pathway is activated by the exposure of cells to stress. The specific role of JNK may depend upon the cellular context. Indeed, the JNK pathway has been implicated in both **apoptosis** and **survival signaling**.

Initial studies demonstrated that JNK contributed to the apoptotic response in neuronal cell death. This role for JNK in stress-induced neuronal cell death has been confirmed in studies of mice with targeted disruption of the neuronal gene *Jnk3*. The *Jnk3* mice are developmentally normal but are severely defective in the apoptotic response to excitotoxins.

The transcriptional targets of the apoptotic JNK signaling pathway have not been established. One potential target is the tumor suppressor **p53**, and another is the transcription factor **c-Myc**. However, the precise roles are unclear.

Mechanism of JNK-Dependent Apoptosis

Recent studies using JNK-null cells have provided a breakthrough. These cells exhibit no defects in Fas-induced apoptosis (death receptor signaling) but show profound defects in stress-induced apoptosis (e.g., from UV radiation). The biochemical defect was localized to the **mitochondria**. The JNK-null cells were defective in the release of **cytochrome c**, which is a critical step in the mitochondrial pathway of apoptosis that leads to the activation of **caspase-9**.

> These data establish that the JNK signaling pathway is required for the response to some, but not all, apoptotic stimuli. JNK is not required for death receptor signaling mediated by caspase-8, but is required for stress-induced apoptosis mediated by the mitochondrial/caspase-9 pathway.

A significant question that remains concerns the molecular mechanism. Potential targets of JNK that may regulate cytochrome c release include members of the **Bcl2** group of apoptotic regulatory proteins.

Role of JNK in Signaling Cell Survival

Although it is established that JNK contributes to some apoptotic responses, it is not clear that apoptosis represents the only functional consequence of JNK activation. The absence of an apoptotic response to JNK activation appears to correlate with the time course—**sustained activation**, but not transient activation, of JNK is associated with apoptosis. Many cytokines cause only transient JNK activation.

The strongest evidence for a survival role comes from the analysis of compound mutant *Jnk1/Jnk2* embryos that exhibit increased apoptosis within the developing forebrain. These data are consistent with the hypothesis that JNK may mediate survival signaling under specific circumstances.

Role of the JNK Signaling Pathway in Embryonic Morphogenesis

Genetic studies of *Drosophila melanogaster* demonstrate that JNK is required for embryonic epithelial cell sheet movements (dorsal closure) and epithelial planar polarity. In the nematode *Caenorhabditis elegans*, JNK is required for the normal function of GABAergic motor neurons. Gene knockout studies in mice also demonstrate that the JNK signaling pathway is required for murine embryonic viability, partly through its role in regulating apoptosis in the developing embryo.

Concluding Remarks

The JNK signal transduction pathway is implicated in many pathological conditions, including cancer, cardiac hypertrophy, ischemia/reperfusion injury, and neurodegenerative diseases, making it a potential target for therapeutic intervention. A key fundamental question that remains unresolved concerns the ability of cells to interpret JNK activation in different ways depending upon context (e.g., survival signaling versus apoptosis). It is likely that this ability is mediated by interactions of JNK with other signaling pathways within the cell.