JNK Signaling Network and Cancer

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Introduction

Jun kinases (JNKs) form a major signaling hub involved in cell proliferation, differentiation, and apoptosis. JNKs belong to the family of mitogen activated protein kinase (MAPK) that is responsive to a variety of environmental stimuli.¹⁻³ Typically, MAP kinase signaling modules progresses through the sequential phosphorylation of constituent MAP-kinase-kinase (MKKK), the MAP kinase kinases (MKKs), and the downstream MAP kinases (MAPKs). MKKKs are serine/threonine kinases that activate MKKs through phosphorylation of serine and threonine residues, whereas MKKs are dual specificity kinases that phosphorylate MAP kinases on serine/threonine and tyrosine residues. Phosphorylated MAP kinases, thus activated, translocate from the cytoplasm to the nucleus where they regulate the activities of specific transcription factors through phosphorylation. The transcription factors activated through such MAP kinase-mediated phosphorylation play a central role in altering the patterns of gene expression associated with different cellular responses to a variety of extracellular stimuli. Thus, the phospho-relay system defined by the 3-tier MKKK-MKK-MAPK modules regulates diverse aspects of cell growth, differentiation, and apoptosis.^{1,4}

Of the 8 distinct MAPK modules that have been characterized thus far in mammalian cells,² JNK signaling module appears to play a role in diverse—often, opposing—cellular responses in a context-specific manner. Their roles in different aspects of tumorigenesis and tumor progression including cancer stem cell maintenance are being fully realized only now. Three distinct isoforms of JNKs, namely, JNK1, JNK2,

and JNK3, have been identified. While JNK1 and JNK2 are present as 4 different splice variants each, JNK3 is represented by 2 splice variants. These different JNK isoforms are activated by 2 distinct upstream MKKs, namely, MKK4 and MKK7. While MKK7, with its 3 distinct splice variants, is specifically involved in the phosphorylation and subsequent activation of JNKs, MKK4 is involved in the activation of both JNKs and p38MAPKs. However, both MKK4 and MKK7 activate JNKs by phosphorylating the threonine and/or tyrosine residues in the T-P-Y motif present in the activation loop of the kinase domains of the JNKs. The MKKs, in turn, are activated by at least 14 different upstream MKKKs (Fig. 1).

From the observation that a disproportionately large number of MKKKs are present in cells to activate just 3 isoforms of JNK via 2 MKKs, namely, MKK4 and MKK7, it has been inferred that specific coupling to different MKKKs, MKKs, and MAPKs are mediated by distinct scaffolding proteins.⁵ The findings that more than 80 distinct protein complexes containing different MKKKs and MKKs that can activate downstream JNKs are indicative of such response-specific JNK-signaling complexes in different physiological contexts.⁶ Thus, it is likely that the observed tumor-promoting effect of the JNK-signaling network in some instances while tumor-suppressing effect of this network in other instances are dependent on the context-specific spatiotemporal regulation of JNK signaling networks defined by the constituents of specific JNK signalosomes. In addition, the cross-talk between the JNK-signaling module and other MAPK-signaling networks such as those of p38MAPK and ERK is likely to

Figure 1. Three-tier JNK signaling module consisting of MKKKs, MKKs, and JNKs. Different configurations of MKKKs, MKKs, or JNKs and spatiotemporal organization of the JNK module facilitated by specific scaffold proteins such as JIP1, JIP2, JIP3, or JLP appear to elicit context-specific cellular responses.

play a dominant role in the genesis and progression of cancer.¹ Thus, further analyses of the spatiotemporal integration of the JNK-signaling network in relation to other signaling networks may finally unravel the mechanism(s) underlying the context-specific role of JNKs in different aspects of cancer cell growth, survival, and metastasis.

In this special issue of *Genes & Cancer*, we have put together 10 reviews that discuss the role of the JNK-signaling network in cancer genesis and progression. The review issue starts with the

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focus on providing a broad overview on the regulation of JNKs, signal integration between JNK and p38MAPK-signaling modules, and dual-specificity phosphatase-mediated regulation of JNKs. This is followed by reviews discussing recently identified novel roles of the JNK-signaling networks in cell cycle control, cancer cell metastasis, and cancer stem cell maintenance. Traversing further through reviews that specifically discuss JNK-signaling networks as targets for cancer therapeutics and their role in resistance to radiation therapy in cancer, the issue concludes with a discussion on the emerging systems biology approach

to analyze the JNK-signaling network. The signaling paradigm that can be inferred from the articles presented here illustrates that the role of JNKs in cancer is primarily defined by the context-specific spatiotemporal integration of signaling inputs from multiple upstream, downstream, and parallel signaling components. Such an understanding can be used to develop novel cancer therapy and/or mitigating strategies for drug as well as radiation resistance in cancer.

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