**Literature review of MKK7**

**Background**

MKK7 is involved in signal transduction mediating the cell responses to proinflammatory cytokines, and environmental stresses (e.g. UV radiation, mitogens, etc.). This kinase specifically activates MAPK8/JNK1 and MAPK9/JNK2 which in turn modify the activity of numerous proteins that reside at the mitochondria or act in the nucleus . MKK7 is ubiquitously expressed in all tissue. However, it displays a higher level of expression in skeletal muscle.

MKK7 works as crucial transducer upstream of JNK signaling. As a result, MKK7 has a great impact on numerous physiological processes such as **proliferation** and **differentiation**, as well as pathological processes such as **apoptosis** and **tumorigenesis**.

**Biological relevance**

In mice models, mkk7−/− embryos die between E11.5 to E13.5 of anemia associated with **abnormal hepatogenesis**[1,2](https://paperpile.com/c/myT405/Wua6+0N9t). Mkk7−/− hepatoblasts display down-regulated expression of the G2/M cell cycle kinase Cdc2[1](https://paperpile.com/c/myT405/Wua6). C-Jun binds to the promoter region of the cdc2 gene. Consequently, **Cdc2 constitutes a potential downstream target** by which the MKK7-JNK-c-Jun signaling pathway regulates cell proliferation.

**Role of MKK7 in heart disease.** The role of MKK7 in cardiac disease was assessed by using a mouse model over-expressing a **dominant active mutant form of MKK7** (MKK7D) in ventricular myocytes[3](https://paperpile.com/c/myT405/dlF0). MKK7D expression led to significant JNK activation. **MKK7D mice exhibited profound diastolic dysfunction and premature death** with signs of **congestive heart failure**. MKK7D mutant hearts were substantially less compliant (elastic). The stiffness was correlated with interstitial fibronectin accumulation. A significant slowing of ventricular electrical conduction in the hearts displaying high levels of JNK activity was the result of a loss of connexin 43 expression and gap junctions, a common hallmark of a failing heart that contributes to arrhythmia. Additionally, Gene array analysis revealed that activation of the MKK7-JNK signaling pathway modulated a number of genes for angiogenesis, potassium regulation and extracellular matrix[4](https://paperpile.com/c/myT405/bxQY).

**Oncogenesis.** NF-kB transcription factors play a crucial role in oncogenesis. NF-κB is aberrantly activated in a wide range of human cancers, in which it promotes survival and malignancy by upregulating antiapoptotic genes. The paradigm of these cancers is multiple myeloma. One of the previously identified downstream transcriptional targets of NF-κB is GADD45β, a selective inhibitor of MKK7 and therefore of apoptosis[5](https://paperpile.com/c/myT405/ZTgJ).

Tornatore *et al.* have found the selective inhibition of GADD45β-MKK7 interaction is a therapeutic target in multiple myeloma by inducing apoptosis in malignant cells[6](https://paperpile.com/c/myT405/Bl6F).

**Relevant targets**

**Neurotoxicity**. Excitotoxicity following cerebral ischemia elicits a molecular cascade, which leads neurons to death. One key molecule of this pathway is c-Jun-N-terminal kinase (JNK), which plays both physiological and pathological roles in neurons. JNK inhibition significantly reduces infarct size and neuronal death[7](https://paperpile.com/c/myT405/7VDn),[8](https://paperpile.com/c/myT405/UIqq). On the other hand, JNK inhibition may have detrimental side effects due to blockade of its physiological function[8,9](https://paperpile.com/c/myT405/UIqq+3ueH).

Several studies have shown that specific inhibition of MKK7 using Gadd45β or its derivatives can abolish MKK7 downstream effects[6](https://paperpile.com/c/myT405/Bl6F),[10](https://paperpile.com/c/myT405/Rwnb). Specific inhibition of MKK7 significantly reduces neuronal death in rat models by excitotoxic cell death, one induced by NMDA exposure and the other by oxygen glucose deprivation[11](https://paperpile.com/c/myT405/WHOb). In both models, blocked MKK7 activation provided significant protection, significantly reducing the infarct size. Further studies support in *in vitro* models the key role **MKK7 inhibition plays in treatment of neurological diseases**[12](https://paperpile.com/c/myT405/Qahf).

**Inflammation.** The c-Jun N-terminal kinase (JNK) is a key regulator of matrix metalloproteinase (MMP) and cytokine production in rheumatoid arthritis (RA) and JNK deficiency markedly protects mice in animal models of arthritis. **Treating mice with anti-sense MKK7 RNA have shown a decrease in symptoms relating to arthritis**[13](https://paperpile.com/c/myT405/jz6G)**.**

**Summary**

MKK7 is involved in cell differentiation and proliferation pathways. While this would implicate MKK7 as an oncogenic target, inhibition of MKK7 **prevents apoptosis**, which is the opposite of what is desired when treating malignant cells.

However, there are conditions where cell-death is not the desired effect, for example, traumatic brain injury where healthy cells die due to surrounding stimuli or in cases of chronic inflammation. Several quality publications support the idea that MKK7 inhibition can be used to mitigate cytotoxicity in neuronal cells. Therefore, **targeting MKK7 could represent a novel therapeutic strategy for several diseases involving JNK activation, specifically involving brain trauma.**

**References**

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