The Tumor Suppressor, $p16^{INK4a}$ Prevents Cell Transformation Through Inhibition of c-Jun Phosphorylation and AP-1 Activity

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$p16^{INK4a}$ is a tumor suppressor protein and inactivation of the *$p16^{INK4a}$* locus is a critical genetic event in the development of human cancers, especially human melanoma skin cancer. However, the molecular basis of the inhibitory effect of $p16^{INK4a}$ on cancer development is not clear. The purpose of these studies was to investigate a possible mechanism explaining the $p16^{INK4a}$ inhibition of neoplastic transformation and UV-induced skin cancer. We demonstrate that the $p16^{INK4a}$ protein suppresses the activity of c-Jun N-terminal kinases (JNKs). The model of the $p16^{INK4a}$-JNK3 complex obtained from protein docking analysis suggests that $p16^{INK4a}$ binds to the glycine-rich loop of the N-terminal domain of JNK3. Although $p16^{INK4a}$ does not affect the phosphorylation of JNKs its interaction with JNK inhibits JNK activity induced by UV exposure. This in turn interferes with cell transformation promoted by the H-Ras-JNK-c-Jun-AP-1 signaling axis.