Regulation of SIRT1 by MAP Kinase Signaling Pathways

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Only within the last decade has the role that histone deacetylases (HDACs) play in the inappropriate silencing of tumor suppressor genes (TSG) emerged as an important theme in cancer biology. The role these enzymes play in the deacetylation of non-histone proteins is also of tremendous interest, as they represent viable targets in the search for novel anti-cancer treatments. The sirtuin proteins are a class of HDACs, which control gene expression. The class III HDAC gene family is referred to as the Silent Information Regulators (or sirtuins). The most prominent sirtuin family member, Sirtuin-1 (SIRT1), has been shown to regulate the lifespan of a number of organisms and has also been shown to be overexpressed in several types of cancers. Very little is known, however, about the mechanisms through which SIRT1 is regulated. This study examined the role that the p38 mitogen-activated protein kinase (MAPK) plays in the regulation of SIRT1. Through this study, it was determined that inhibition of p38 activity leads to an increase in the steady-state protein levels of SIRT1. Additionally, it was observed that p38 binds to SIRT1 *in vivo* and that its inhibition causes a reduction in the phosphorylation of SIRT1. These findings are the first to identify an upstream protein kinase that negatively regulates SIRT1.