Oxidative Stress Induced Senescence


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**Introduction**

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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**Literature references**


Reactome database release: 72

This document contains 1 pathway and 40 reactions (see Table of Contents)
Oxidative stress, caused by increased concentration of reactive oxygen species (ROS) in the cell, can happen as a consequence of mitochondrial dysfunction induced by the oncogenic RAS (Moiseeva et al. 2009) or independent of oncogenic signaling. Prolonged exposure to interferon-beta (IFNB, IFN-beta) also results in ROS increase (Moiseeva et al. 2006). ROS oxidize thioredoxin (TXN), which causes TXN to dissociate from the N-terminus of MAP3K5 (ASK1), enabling MAP3K5 to become catalytically active (Saitoh et al. 1998). ROS also stimulate expression of Ste20 family kinases MINK1 (MINK) and TNIK through an unknown mechanism, and MINK1 and TNIK positively regulate MAP3K5 activation (Nicke et al. 2005).

MAP3K5 phosphorylates and activates MAP2K3 (MKK3) and MAP2K6 (MKK6) (Ichijo et al. 1997, Takekawa et al. 2005), which act as p38 MAPK kinases, as well as MAP2K4 (SEK1) (Ichijo et al. 1997, Matsura et al. 2002), which, together with MAP2K7 (MKK7), acts as a JNK kinase.


Phosphorylation of JNKs (MAPK8, MAPK9 and MAPK10) by MAP3K5-activated MAP2K4 (Deacon and Blank 1997, Fleming et al. 2000) allows JNKs to migrate to the nucleus (Mizukami et al. 1997) where they phosphorylate JUN. Phosphorylated JUN binds FOS phosphorylated by ERK1 or ERK2, downstream of activated RAS (Okazaki and Sagata 1995, Murphy et al. 2002), forming the activated protein 1 (AP-1) complex (FOS:JUN heterodimer) (Glover and Harrison 1995, Ainbinder et al. 1997).
Activation of p38 MAPKs and JNKs downstream of MAP3K5 (ASK1) ultimately converges on transcriptional regulation of CDKN2A locus. In dividing cells, nucleosomes bound to the CDKN2A locus are trimethylated on lysine residue 28 of histone H3 (HIST1H3A) by the Polycomb repressor complex 2 (PRC2), creating the H3K27Me3 (Me3K-28-HIST1H3A) mark (Bracken et al. 2007, Kotake et al. 2007). The expression of Polycomb constituents of PRC2 (Kuzmichev et al. 2002) - EZH2, EED and SUZ12 - and thereby formation of the PRC2, is positively regulated in growing cells by E2F1, E2F2 and E2F3 (Weinmann et al. 2001, Bracken et al. 2003). H3K27Me3 mark serves as a docking site for the Polycomb repressor complex 1 (PRC1) that contains BMI1 (PCGF4) and is therefore named PRC1.4, leading to the repression of transcription of p16INK4A and p14ARF from the CDKN2A locus, where PRC1.4 mediated repression of p14ARF transcription in humans may be context dependent (Voncken et al. 2005, Dietrich et al. 2007, Agherbi et al. 2009, Gao et al. 2012). MAPKAPK2 and MAPKAPK3, activated downstream of the MAP3K5-p38 MAPK cascade, phosphorylate BMI1 of the PRC1.4 complex, leading to dissociation of PRC1.4 complex from the CDKN2A locus and upregulation of p14ARF transcription (Voncken et al. 2005). AP-1 transcription factor, formed as a result of MAP3K5-JNK signaling, as well as RAS signaling, binds the promoter of KDM6B (JMJD3) gene and stimulates KDM6B expression. KDM6B is a histone demethylase that removes H3K27Me3 mark i.e. demethylates lysine K28 of HIST1H3A, thereby preventing PRC1.4 binding to the CDKN2A locus and allowing transcription of p16INK4A (Agger et al. 2009, Barradas et al. 2009, Lin et al. 2012).

p16INK4A inhibits phosphorylation-mediated inactivation of RB family members by CDK4 and CDK6, leading to cell cycle arrest (Serrano et al. 1993). p14ARF inhibits MDM2-mediated degradation of TP53 (p53) (Zhang et al. 1998), which also contributes to cell cycle arrest in cells undergoing oxidative stress. In addition, phosphorylation of TP53 by MAPKAPK5 (PRAK) activated downstream of MAP3K5-p38 MAPK signaling, activates TP53 and contributes to cellular senescence (Sun et al. 2007).

Literature references


Editions

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RAS signaling and prolonged interferon-beta stimulation promote generation of reactive oxygen species (ROS)

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