Oncogene Induced Senescence

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19/08/2019
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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 69

This document contains 1 pathway and 18 reactions (see Table of Contents)
Oncogene-induced senescence (OIS) is triggered by high level of RAS/RAF/MAPK signaling that can be caused, for example, by oncogenic mutations in RAS or RAF proteins, or by oncogenic mutations in growth factor receptors, such as EGFR, that act upstream of RAS/RAF/MAPK cascade. Oncogene-induced senescence can also be triggered by high transcriptional activity of E2F1, E2F2 or E2F3 which can be caused, for example, by the loss-of-function of RB1 tumor suppressor.

Oncogenic signals trigger transcription of CDKN2A locus tumor suppressor genes: p16INK4A and p14ARF. p16INK4A and p14ARF share exons 2 and 3, but are expressed from different promoters and use different reading frames (Quelle et al. 1995). Therefore, while their mRNAs are homologous and are both translationally inhibited by miR-24 microRNA (Lal et al. 2008, To et al. 2012), they share no similarity at the amino acid sequence level and perform distinct functions in the cell. p16INK4A acts as the inhibitor of cyclin-dependent kinases CDK4 and CDK6 which phosphorylate and inhibit RB1 protein thereby promoting G1 to S transition and cell cycle progression (Serrano et al. 1993). Increased p16INK4A level leads to hypophosphorylation of RB1, allowing RB1 to inhibit transcription of E2F1, E2F2 and E2F3-target genes that are needed for cell cycle progression, which results in cell cycle arrest in G1 phase. p14-ARF binds and destabilizes MDM2 ubiquitin ligase (Zhang et al. 1998), responsible for ubiquitination and degradation of TP53 (p53) tumor suppressor protein (Wu et al. 1993, Fuchs et al. 1998, Fang et al. 2000). Therefore, increased p14-ARF level leads to increased level of TP53 and increased expression of TP53-target genes, such as p21, which triggers p53-mediated cell cycle arrest and, depending on other factors, may also lead to p53-mediated apoptosis. CDKN2B locus, which encodes an inhibitor of CDK4 and CDK6, p15INK4B, is located in the vicinity of CDKN2A locus, at the chromosome band 9p21. p15INK4B, together with p16INK4A, contributes to senescence of human T-lymphocytes (Erickson et al. 1998) and mouse fibroblasts (Malumbres et al. 2000). SMAD3, activated by TGF-beta-1 signaling, controls senescence in the mouse multistage carcinogenesis model through regulation of MYC and p15INK4B gene expression (Vijayachandra et al. 2003). TGF-beta-induced p15INK4B expression is also important for the senescence of hepatocellular carcinoma cell lines (Senturk et al. 2010).
MAP kinases MAPK1 (ERK2) and MAPK3 (ERK1), which are activated by RAS signaling, phosphorylate ETS1 and ETS2 transcription factors in the nucleus (Yang et al. 1996, Seidel et al. 2002, Foulds et al. 2004, Nelson et al. 2010). Phosphorylated ETS1 and ETS2 are able to bind RAS response elements (RREs) in the CDKN2A locus and stimulate p16INK4A transcription (Ohtani et al. 2004). At the same time, activated ERKs (MAPK1 i.e. ERK2 and MAPK3 i.e. ERK1) phosphorylate ERF, the repressor of ETS2 transcription, which leads to translocation of ERF to the cytosol and increased transcription of ETS2 (Sgouras et al. 1995, Le Gallic et al. 2004). ETS2 can be sequestered and inhibited by binding to ID1, resulting in inhibition of p16INK4A transcription (Ohtani et al. 2004).

Transcription of p14ARF is stimulated by binding of E2F transcription factors (E2F1, E2F2 or E2F3) in complex with SP1 to p14ARF promoter (Parisi et al. 2002).

Oncogenic RAS signaling affects mitochondrial metabolism through an unknown mechanism, leading to increased generation of reactive oxygen species (ROS), which triggers oxidative stress induced senescence pathway. In addition, increased rate of cell division that is one of the consequences of oncogenic signaling, leads to telomere shortening which acts as another senescence trigger.

While OIS has been studied to considerable detail in cultured cells, establishment of in vivo role of OIS has been difficult due to lack of specific biomarkers and its interconnectedness with other senescence pathways (Baek and Ryeom 2017, reviewed in Sharpless and Sherr 2015).

**Literature references**


**Editions**

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MAPKs phosphorylate ETS1 and ETS2

**Location:** Oncogene Induced Senescence

**Stable identifier:** R-HSA-3132737

**Type:** transition

**Compartments:** nucleoplasm

Both ETS1 and ETS2 contain a consensus site (PLLTP) for MAPK3 and MAPK1 (ERK1 and ERK2, respectively) in the vicinity of the pointed domain, while the pointed domain contains a docking site needed for ERK1/2 binding to ETS1/2. ETS1 and ETS2 are able to collaborate with RAS in superactivating the promoters that contain RREs (RAS response elements) that include ETS-binding sites. The cooperation of ETS1 and ETS2 with RAS activation is dependent on the phosphorylation of PLLTP threonine residue (T38 in ETS1; T72 in ETS2) (Yang et al. 1996, Seidel et al. 2002). Phosphorylation of ETS1 and ETS2 by ERK1/2 induces a conformational change that increases their affinity for the TAZ domain of the transcriptional coactivator CREBBP (CBP) and the transcriptional activation of RREs (Foulds et al. 2004, Nelson et al. 2010), although ETS1/ETS2 may interact with CREBBP in the absence of phosphorylation (Jayaraman et al. 1999). Phosphorylation of serine residue S41 of ETS1 (corresponds to serine residue S75 of ETS2) may be necessary for full activation of ETS1/2 (Nelson et al. 2010).

**Followed by:** ID1 sequesters ETS2, Phosphorylated ETS1 binds p16INK4A promoter, Phosphorylated ETS2 binds p16INK4A promoter

**Literature references**


Phosphorylated ETS1 binds p16INK4A promoter

Location: Oncogene Induced Senescence

Stable identifier: R-HSA-3200023

Type: binding

Compartments: nucleoplasm

ETS1 and ETS2, activated by RAS/RAF/MAP kinase cascade, bind the promoter of p16INK4A in the CDKN2A locus (Ohtani et al. 2001). CDKN2A locus also encodes p14ARF (p19ARF in mouse), but from a different promoter and in a different reading frame. While p16INK4A and p14ARF use different exon 1, (exon 1-alpha and exon 1-beta, respectively), they share exons 2 and 3. However, because the reading frames are different, there is no amino acid sequence similarity between the two proteins (Quelle et al. 1995).

Preceded by: MAPKs phosphorylate ETS1 and ETS2

Followed by: p-T38-ETS1/p-T72-ETS2 stimulates transcription of p16INK4A mRNA

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Phosphorylated ETS2 binds p16INK4A promoter

**Location:** Oncogene Induced Senescence

**Stable identifier:** R-HSA-8979082

**Type:** binding

**Compartments:** nucleoplasm

ETS2, activated by RAS/RAF/MAP kinase cascade, binds the promoter of p16INK4A in the CDKN2A locus (Ohtani et al. 2001). CDKN2A locus also encodes p14ARF (p19ARF in mouse), but from a different promoter and in a different reading frame. While p16INK4A and p14ARF use different exon 1, (exon 1-alpha and exon 1-beta, respectively), they share exons 2 and 3. However, because the reading frames are different, there is no amino acid sequence similarity between the two proteins (Quelle et al. 1995).

**Preceded by:** MAPKs phosphorylate ETS1 and ETS2

**Followed by:** p-T38-ETS1/p-T72-ETS2 stimulates transcription of p16INK4A mRNA

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p-T38-ETS1/p-T72-ETS2 stimulates transcription of p16INK4A mRNA

**Location:** Oncogene Induced Senescence

**Stable identifier:** R-HSA-3209098

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

Phosphorylated ETS1 and ETS2 stimulate p16INK4A transcription, resulting in cell cycle arrest with arrested cells exhibiting high p16INK4A level and senescence-associated beta-galactosidase activity. It is possible that ETS2 is the main transmitter of RAS signaling to p16INK4A at the initiation of the senescence program, and that ETS1 maintains high p16INK4A level once the senescence is already established (Ohtani et al. 2001).

**Preceded by:** Phosphorylated ETS1 binds p16INK4A promoter, Phosphorylated ETS2 binds p16INK4A promoter

**Followed by:** miR-24 binds p16INK4A and p14ARF mRNAs

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**ID1 sequesters ETS2**

**Location:** Oncogene Induced Senescence

**Stable identifier:** R-HSA-3209165

**Type:** binding

**Compartments:** nucleoplasm

Binding of ID1 to ETS2 inhibits ETS2-mediated activation of p16INK4A transcription (Ohtani et al. 2001).

**Preceded by:** MAPKs phosphorylate ETS1 and ETS2

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ERF binds ETS2 promoter

**Location:** Oncogene Induced Senescence

**Stable identifier:** R-HSA-3209177

**Type:** binding

**Compartments:** nucleoplasm

ERF binds to an ETS-binding site in the ETS2 promoter (Sgouras et al. 1995). Phosphorylation of ERF by activated MAPK1 (ERK2) or MAPK3 (ERK1) interferes with ERF-mediated upregulation of ETS2 (Le Gallic et al. 2004).

**Followed by:** ERF inhibits ETS2 expression

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ERF inhibits ETS2 expression

Location: Oncogene Induced Senescence

Stable identifier: R-HSA-3209179

Type: omitted

Compartments: nucleoplasm

Binding of ERF to ETS2 promoter strongly represses ETS2 transcription (Sgouras et al. 1995).

Preceded by: ERF binds ETS2 promoter

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Activated ERKs phosphorylate ERF

**Location:** Oncogene Induced Senescence

**Stable identifier:** R-HSA-3209160

**Type:** transition

**Compartments:** nucleoplasm

**Inferred from:** Mapk1 (Erk2) phosphorylates ERF (Homo sapiens)

Activated ERKs (ERK1 i.e. MAPK3 and ERK2 i.e. MAPK1) phosphorylate ERF on threonine residue T526 and possibly other sites. The threonine T526 seems to be the dominant phosphorylation site and its functional relevance has been established (Sgouras et al. 1995, Le Gallic et al. 2004).

**Followed by:** Phosphorylated ERF translocates to the cytosol

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Phosphorylated ERF translocates to the cytosol

**Location:** Oncogene Induced Senescence

**Stable identifier:** R-HSA-3209159

**Type:** transition

**Compartments:** nucleoplasm, cytosol

Phosphorylation of ERF at threonine TS26 by activated ERKs triggers ERF export from the nucleus to the cytosol (Le Gallic et al. 2004), which is expected to relieve ERF-mediated inhibition of ETS2 transcription.

**Preceded by:** Activated ERKs phosphorylate ERF

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Association of INK4 family proteins with CDK4/6

**Location:** Oncogene Induced Senescence

**Stable identifier:** R-HSA-182594

**Type:** binding

**Compartments:** cytosol

Prior to mitogen activation, the inhibitory proteins of the INK4 family (p15, p16, p18, and p19) associate with the catalytic domains of free CDK4 and CDK6, preventing their association with D type cyclins (CCND1, CCND2 and CCND3), and thus their activation and their inhibitory phosphorylation of the RB family (Serrano et al. 1993, Hannon and Beach 1994, Guan et al. 1994, Guan et al. 1996, Parry et al. 1995). Inactivation and defects of RB1 strongly upregulate p16INK4A (Parry et al. 1995).

**Preceded by:** Translation of p16INK4A mRNA is inhibited by miR-24

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E2F1, E2F2, or E2F3 and SP1 bind p14ARF promoter

**Location:** Oncogene Induced Senescence

**Stable identifier:** R-HSA-3209096

**Type:** binding

**Compartments:** nucleoplasm

E2F1, E2F2 or E2F3 forms a complex with the transcription factor SP1 on p14-ARF promoter (Parisi et al. 2002).

**Followed by:** E2F1/E2F2/E2F3 and SP1 stimulate transcription of p14ARF mRNA

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E2F1/E2F2/E2F3 and SP1 stimulate transcription of p14ARF mRNA

**Location:** Oncogene Induced Senescence

**Stable identifier:** R-HSA-3209109

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

E2F1, E2F2 or E2F3 in complex with SP1 stimulates p14ARF transcription (Parisi et al. 2002). Therefore, increased activity of E2F1, E2F2 or E2F3, which may result from the loss of function of the tumor suppressor protein RB1, an inhibitor of E2F1/2/3, leads to an increased level of p14ARF (Komori et al. 2005).

**Preceded by:** E2F1, E2F2, or E2F3 and SP1 bind p14ARF promoter

**Followed by:** miR-24 binds p16INK4A and p14ARF mRNAs

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miR-24 binds p16INK4A and p14ARF mRNAs

Location: Oncogene Induced Senescence

Stable identifier: R-HSA-3209151

Type: binding

Compartments: cytosol

MicroRNA miR-24 is able to bind both p16INK4A mRNA (Lal et al. 2008) and p14ARF mRNA (To et al. 2012) through their shared 3'UTR. miR-24 inhibits translation of p16INK4A and p14ARF mRNAs, but does not induce mRNA degradation, resulting in expression of high levels of p16INK4A and p14ARF transcripts, while protein levels of p16INK4A and p14ARF are low (Lal et al. 2008, To et al. 2012).

Preceded by: E2F1/E2F2/E2F3 and SP1 stimulate transcription of p14ARF mRNA, p-T38-ETS1/p-T72-ETS2 stimulates transcription of p16INK4A mRNA

Followed by: Translation of p14ARF mRNA is inhibited by miR-24, Translation of p16INK4A mRNA is inhibited by miR-24

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Translation of p14ARF mRNA is inhibited by miR-24

Location: Oncogene Induced Senescence

Stable identifier: R-HSA-3209111

Type: omitted

Compartments: cytosol, nucleoplasm

MicroRNA miR-24 inhibits translation of p14ARF mRNA without causing mRNA degradation. This results in high p14ARF transcript level accompanied by low p14ARF protein level (To et al. 2012).

Preceded by: miR-24 binds p16INK4A and p14ARF mRNAs

Followed by: p14ARF forms a ternary complex with MDM2 and TP53

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Translation of p16INK4A mRNA is inhibited by miR-24

Location: Oncogene Induced Senescence

Stable identifier: R-HSA-3209114

Type: omitted

Compartments: cytosol

MicroRNA miR-24 inhibits translation of p16INK4A mRNA without causing mRNA degradation. This results in high p16INK4A transcript level accompanied by low p16INK4A protein level (Lal et al. 2008).

Preceded by: miR-24 binds p16INK4A and p14ARF mRNAs

Followed by: Association of INK4 family proteins with CDK4/6

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MDM2 ubiquitinates TP53

**Location:** Oncogene Induced Senescence

**Stable identifier:** R-HSA-6804879

**Type:** transition

**Compartments:** nucleoplasm

MDM2 is an ubiquitin ligase whose expression is positively regulated by TP53 (p53) (Wu et al. 1993). MDM2 binds TP53 tetramer (Maki 1999) and promotes its ubiquitination and subsequent degradation (Fuchs et al. 1998). Formation of MDM2 homodimers (Cheng et al. 2011) or heterodimers with MDM4 (MDMX) is needed for efficient ubiquitination of TP53 (Linares et al. 2003). While MDM2-TP53 binding occurs at the amino-terminus of TP53, MDM2 ubiquitinates TP53 lysine residues at the carboxy-terminus. Acetylation of those lysines can inhibit MDM2-dependent ubiquitination (Li et al. 2002).

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p14ARF forms a ternary complex with MDM2 and TP53

Location: Oncogene Induced Senescence

Stable identifier: R-HSA-6804998

Type: binding

Compartments: nucleoplasm

p14ARF forms a complex with TP53-bound MDM2 by interacting with the C-terminus of MDM2, while the N-terminus of MDM2 is involved in TP53 (p53) binding. p14ARF cannot associate with TP53 in the absence of MDM2 (Zhang et al. 1998).

Preceded by: Translation of p14ARF mRNA is inhibited by miR-24

Followed by: p14ARF sequesters MDM2

Literature references


Editions

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**p14ARF sequesters MDM2**

**Location:** Oncogene Induced Senescence

**Stable identifier:** R-HSA-6804996

**Type:** dissociation

**Compartments:** nucleoplasm

Binding of p14ARF to MDM2 decreases the half-life of MDM2, likely through promoting MDM2 degradation. Thus, p14ARF inhibits MDM2-mediated ubiquitination and degradation of TP53 (Zhang et al. 1998).

**Preceded by:** p14ARF forms a ternary complex with MDM2 and TP53

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