The role of GTSE1 in G2/M progression after G2 checkpoint

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11/07/2020
Introduction

Reactome is an 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: 73

This document contains 1 pathway and 10 reactions (see Table of Contents)
GTSE1 (B99) was identified as a microtubule-associated protein product of the mouse B99 gene, which exhibits both a cell cycle regulated expression, with highest levels in G2, and DNA damage triggered expression under direct control of TP53 (p53) (Utrera et al. 1998, Collavin et al. 2000). Human GTSE1, similar to the mouse counterpart, binds to microtubules, shows cell cycle regulated expression with a peak in G2 and plays a role in G2 checkpoint recovery after DNA damage but is not transcriptionally regulated by TP53 (Monte et al. 2003, Monte et al. 2004, Scolz et al. 2012).

In G1 cells, GTSE1 is found at the microtubule lattice, likely due to direct binding to tubulin. An evolutionarily conserved interaction between GTSE1 and MAPRE1 (EB1), a microtubule plus end protein, promotes GTSE1 localization to the growing tip of the microtubules, which contributes to cell migration and is likely involved in cancer cell invasiveness. Highly invasive breast cancer cell lines exhibit high GTSE1 levels in G1, while GTSE1 levels in G1 are normally low. At the beginning of mitotic prometaphase, GTSE1 is phosphorylated by mitotic kinase(s), possibly CDK1, in proximity to the MAPRE1-binding region, causing GTSE1 dissociation from the plus end microtubule ends (Scolz et al. 2012).

During G2 checkpoint recovery (cell cycle re-entry after DNA damage induced G2 arrest), GTSE1 relocates to the nucleus where it binds TP53 and, in an MDM2-dependent manner, promotes TP53 cytoplasmic translocation and proteasome mediated degradation (Monte et al. 2003, Monte et al. 2004). Relocation of GTSE1 to the nucleus in G2 phase depends on PLK1-mediated phosphorylation of GTSE1 (Liu et al. 2010).

GTSE1-facilitated down-regulation of TP53 in G2 allows cells to avoid TP53 mediated apoptosis upon DNA damage and to re-enter cell cycle (Monte et al. 2003). While TP53 down-regulation mediated by GTSE1 in G2 correlates with decreased expression of TP53 target genes involved in apoptosis and cell cycle arrest, GTSE1 can also increase the half-life of the TP53 target p21 (CDKN1A). GTSE1-mediated stabilization of
CDKN1A involves interaction of GTSE1 with CDKN1A and its chaperone complex, consisting of HSP90 and FKBPL (WISP39), and may be involved in resistance to paclitaxel treatment (Bublik et al. 2010).

**Literature references**


**Editions**

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https://reactome.org
GTSE1 binds microtubule lattice in interphase cells

**Location:** The role of GTSE1 in G2/M progression after G2 checkpoint

**Stable identifier:** R-HSA-8852280

**Type:** binding

**Compartments:** cytosol

In interphase cells, GTSE1 localizes to the microtubule lattice, probably due to direct binding to tubulin (Scolz et al. 2012).

**Literature references**


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GTSE1 binds MAPRE1 (EB1) at microtubule plus ends

Location: The role of GTSE1 in G2/M progression after G2 checkpoint

Stable identifier: R-HSA-8852298

Type: binding

Compartments: cytosol

During interphase, GTSE1 localizes to the growing plus-end tip of microtubules by binding to the microtubule plus end protein MAPRE1 (EB1). This interaction involves two SKIP-like EB1-interaction motifs of GTSE1 and the C-terminal EB-homology (EBH) domain of MAPRE1. The interaction between GTSE1 and MAPRE1 is evolutionarily conserved. The interaction between GTSE1 and MAPRE1 at growing microtubule plus ends promotes cell migration, likely through microtubule-induced disassembly of focal adhesions. GTSE1 expression levels in G1 phase correlate with invasiveness of breast cancer cell lines (Scolz et al. 2012).

Followed by: Mitotic phosphorylation-induced dissociation of GTSE1 from microtubule plus ends

Literature references

Mitotic phosphorylation-induced dissociation of GTSE1 from microtubule plus ends

Location: The role of GTSE1 in G2/M progression after G2 checkpoint

Stable identifier: R-HSA-8852306

Type: transition

Compartments: cytosol

Starting in mitotic prometaphase, GTSE1 becomes phosphorylated at threonine residues T513 and T526 (and possibly other sites), located adjacent to the two SKIP-like motifs involved in binding to MAPRE1 (EB1). Mitotic phosphorylation of GTSE1 inhibits its association with microtubule plus ends. CDK1 activity inhibits the association of recombinant human GTSE1 with microtubule plus ends in Xenopus extracts, but it is not certain whether CDK1 or another mitotic kinase phosphorylates GTSE1 (Scolz et al. 2012).

Preceded by: GTSE1 binds MAPRE1 (EB1) at microtubule plus ends

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https://reactome.org
GTSE1 binds PLK1

**Location:** The role of GTSE1 in G2/M progression after G2 checkpoint

**Stable identifier:** R-HSA-8852324

**Type:** binding

**Compartments:** cytosol

GTSE1 binds PLK1. The two proteins co-localize on centrosomes from G2 phase to prophase, but not after metaphase (Liu et al. 2010).

**Followed by:** PLK1 phosphorylates GTSE1

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Activated PLK1 phosphorylates GTSE1 on serine residue S435, located in immediate vicinity of the GTSE1 nuclear localization signal (NLS) R431RR433 (Arg431Arg432Arg433). PLK1-mediated phosphorylation promotes GTSE1 nuclear translocation, possibly by exposing the NLS of GTSE1 to the nuclear import machinery. PLK1 can also phosphorylate human GTSE1 on serine residue S233. S233 is not evolutionarily conserved and is therefore not shown (Liu et al. 2010).

**Preceded by:** GTSE1 binds PLK1  
**Followed by:** GTSE1 translocates to the nucleus

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GTSE1 translocates to the nucleus

**Location:** The role of GTSE1 in G2/M progression after G2 checkpoint

**Stable identifier:** R-HSA-8852331

**Type:** transition

**Compartments:** cytosol, nucleoplasm

PLK1-mediated phosphorylation of GTSE1 is needed for nuclear accumulation of GTSE1, probably because it exposes the nuclear localization signal (NLS) of GTSE1 to the nuclear import machinery. Nuclear localization of GTSE1 is not needed for normal G2 phase progression, but is needed for the G2 checkpoint recovery (cell cycle re-entry after G2 checkpoint arrest) (Liu et al. 2010).

**Preceded by:** PLK1 phosphorylates GTSE1

**Followed by:** GTSE1 binds TP53

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https://reactome.org
GTSE1 binds TP53

Location: The role of GTSE1 in G2/M progression after G2 checkpoint

Stable identifier: R-HSA-8852337

Type: binding

Compartments: nucleoplasm

Since MDM2-mediated ubiquitination of TP53 promotes translocation of TP53 to the cytosol, and since GTSE1-facilitated translocation of TP53 to the cytosol depends on the functional MDM2 (with no reported interaction between GTSE1 and MDM2) (Monte et al. 2004), it is plausible that GTSE1 binds to TP53 polyubiquitinated by MDM2. The interaction between TP53 and GTSE1 involves the C-terminal regulatory domain of TP53 and the C-terminus of GTSE1 (Monte et al. 2003).

Preceded by: GTSE1 translocates to the nucleus

Followed by: GTSE1 promotes translocation of TP53 to the cytosol

Literature references


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GTSE1 promotes translocation of TP53 to the cytosol

**Location:** The role of GTSE1 in G2/M progression after G2 checkpoint

**Stable identifier:** R-HSA-8852351

**Type:** transition

**Compartments:** cytosol, nucleoplasm

Binding of GTSE1 to TP53 (p53) in the nucleus promotes translocation of TP53 to the cytosol. This process is dependent on the nuclear export signal (NES) of GTSE1 (Monte et al. 2004).

**Preceded by:** GTSE1 binds TP53

**Followed by:** GTSE1 facilitates proteasome-mediated degradation of TP53

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GTSE1 facilitates proteasome-mediated degradation of TP53

**Location:** The role of GTSE1 in G2/M progression after G2 checkpoint

**Stable identifier:** R-HSA-8852354

**Type:** omitted

**Compartments:** cytosol

GTSE1 promotes down-regulation of TP53 in a proteasome-dependent way. Nuclear export of TP53 facilitated by GTSE1 and MDM2 likely makes ubiquitinated TP53 available to the proteasome machinery. GTSE1-mediated decrease of TP53 levels is needed for the G2 checkpoint recovery (cell cycle re-entry after DNA damage induced G2 arrest) and rescues cells from DNA damage induced apoptosis during S/G2 phase (Monte et al. 2003, Monte et al. 2004).

**Preceded by:** GTSE1 promotes translocation of TP53 to the cytosol

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GTSE1 binds CDKN1A

Location: The role of GTSE1 in G2/M progression after G2 checkpoint

Stable identifier: R-HSA-8852362

Type: binding

Compartments: cytosol

Stabilization of the newly synthesized protein product of the CDKN1A (p21) gene, a CDK inhibitor and a TP53 (p53) transcriptional target, requires binding of CDKN1A to FKBPL (WISp39). FKBPL simultaneously interacts with CDKN1A and a chaperone protein HSP90, forming a ternary complex (Jascur et al. 2005). GTSE1 was identified as another component of the complex of CDKN1A, FKBPL and HSP90. GTSE1 directly interacts with CDKN1A and FKBPL and contributes to CDKN1A stabilization (Bublik et al. 2010). Increased CDKN1A levels delay G2/M onset and rescue cells from G2 checkpoint-induced apoptosis, thus causing resistance to taxol induced cytotoxicity (Yu et al. 1998, Bublik et al. 2010).

Literature references


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   - GTSE1 binds PLK1
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   - GTSE1 translocates to the nucleus
   - GTSE1 binds TP53
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   - GTSE1 facilitates proteasome-mediated degradation of TP53
   - GTSE1 binds CDKN1A

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