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Gene Section
Short Communication

CLSPN (claspin)

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Identity

HGNC (Hugo): CLSPN

Location: 1p34.3

Note

Claspin is a S-phase checkpoint factor that is activated in response to replication stress or other DNA damage induced by genotoxic agents.

DNA/RNA

Description

The gene spans approximately 37 kb and contains 25 exons.

Transcription

There are different transcripts variants, five of them encode for different isoforms. Two transcript variants encode for known proteins. The transcript variant 1 of 4769 bp counts 25 exons. The transcript variant 2 of 3977 bp, counts 24 exons (lacks 1 exon maintaining the frame).

Protein

Note

The transcript variant 1 encodes for a protein of 1339 aminoacids.
The transcript variant 2 encodes for a protein of 1275 amino acids.

Expression

Claspin peaks at S/G2 phase in response to DNA replication blocks and DNA damage.

Localisation

Claspin is located in the nucleus and it associates with Chk1 following replication fork stress or other types of DNA damage.

Function

Claspin is a S-phase checkpoint regulator required in response to DNA replication stress and to DNA damage induced by UV and irradiation (Chini and Chen, 2003; Sar et al., 2004; Freire et al., 2006; Tanaka, 2010).

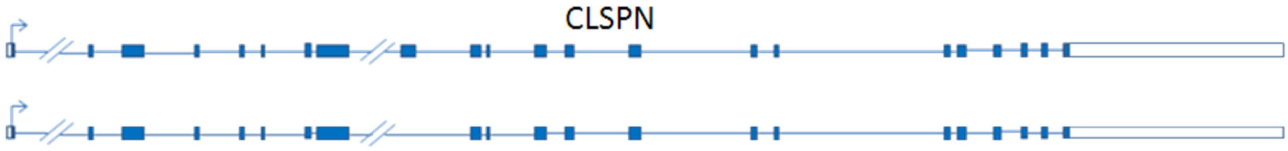

Figure 1. Schematic representation of the Claspin with the two transcript variants. The transcript variant 1 with 25 exons and the transcript variant 2 with 24 exons. The exons are indicated by boxes and introns by lines.

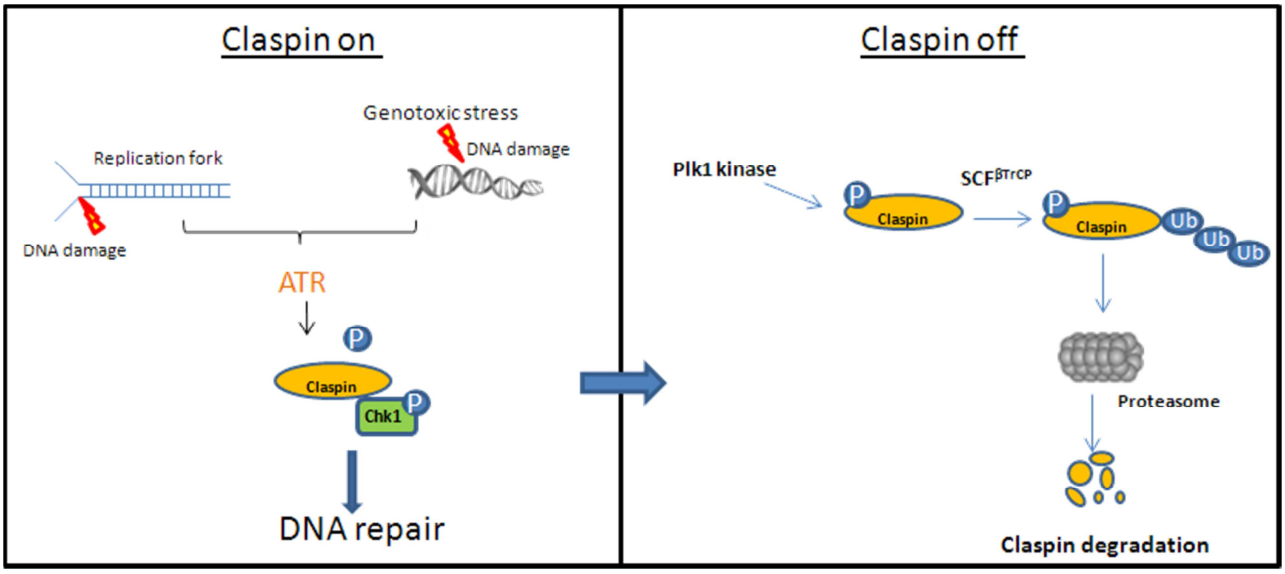

Figure 2. Claspin regulation during DNA damage checkpoint response pathway. Upon DNA damage, ATR activates Claspin, promoting the activation of the effector kinase Chk1. Once the damage is repaired, Plk1 binds and phosphorylates Claspin favoring its proteasomal degradation.

Claspin is a mediator of ATR-Chk1 signaling cascade triggers for cell cycle checkpoint activation in DNA damage response.
Claspin becomes phosphorylated and interacts with Chk1 promoting its activation by ATR-dependent phosphorylation (Chini and Chen, 2004; Kumagai and Dunphy, 2003; Clarke and Clarke, 2005).
Claspin also interacts with the checkpoint proteins ATR and RAd9, and ATR regulates Claspin phosphorylation in presence of DNA damage induced by genotoxic stress including UV, IR and hydroxyurea, resulting in recruitment and phosphorylation of BRCA1 (Jeong et al., 2003; Lin et al., 2004; Sørensen et al., 2004).
When DNA damage has been repaired, Claspin response is turned off by ubiquitin proteasome pathway in order to inactivate checkpoint response and facilitate cells to enter the cell cycle.
Therefore Claspin is phosphorylated by Plk1 kinase to permit its interaction with SCF$^{\beta TrCP}$ ubiquitin ligase that promotes its degradation (Mailand et al., 2006; Mamely et al., 2006; Peschiaroli et al., 2006). Claspin has also been found associated to replication forks in absence of DNA damage suggesting a function as a sensor required for replication fork stability (Sørensen et al., 2004; Petermann et al., 2008; Scorah et al., 2009).
Finally it has been observed a role of the Claspin in genome stability.
Inhibition of the Claspin by RNA interference leads to both chromosome alterations and fragile site expression in human cells. Following aphidicolin treatment, Claspin increases due to its requirement to checkpoint activation, while its synthesis decrement after a prolonged aphidicolin treatment.
It has been proposed that, following an extreme replication block, Claspin allows rare cells to escape checkpoint mechanisms and enter mitosis although their genome has not yet fully replicated (Focarelli et al., 2009).

Homology

This gene is present in S. cerevisiae as scMrc1; in S. pombe as spMrc1; in vertebrates as Claspin.

Mutations

Germinal

- First study that reports the mutation screening of the CLSPN gene in familial breast cancer cases identifying different sequence changes (Erkko et al., 2008).
Nevertheless no of these mutations is related to breast cancer susceptibility.
- Sequence variants of Claspin have been identified in different human cancers. Eight nonsynonymous variants were found from the germline of two cancer-prone individuals and five cancer cells lines of breast, ovarian, and hematopoietic origin (Zhang et al., 2009).

Implicated in

Various cancers

Note

Claspin expression levels increased in cancer cells lines and tumor specimens in a study performed in normal fibroblasts and various cancer cell lines, and from tumor and normal tissues of patients with primary epithelial carcinomas, in order to evaluate Claspin as a proliferation marker (Tsimaratou et al., 2007).

Breast cancer

Note

Transcript levels of Claspin were highly detected in tumor breast cancer tissues in which estrogen receptor

and progesterone receptor was lost (Verlinden et al., 2007).

Cervical cancer

Note

Claspin expression is found significantly high in cervical cancer cell lines and the analysis of its expression could be clinically relevant in the diagnosis of Human Papillomavirus-related high grade lesions of uterine cervix (Benevolo et al., 2012).

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