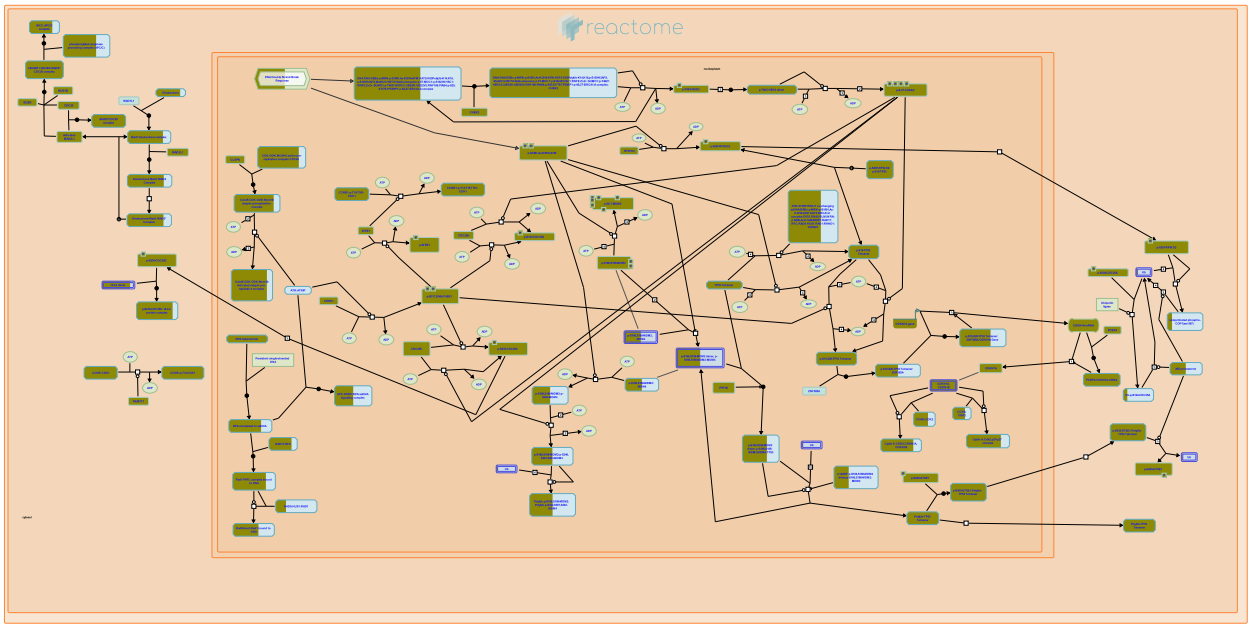
Cell Cycle Checkpoints



Hardwick, KG., Hoffmann, I., Khanna, KK., Knudsen, E., Matthews, L., O'Donnell, M., Sanchez, Y., Walworth, N., Yen, TJ.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

16/05/2024

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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

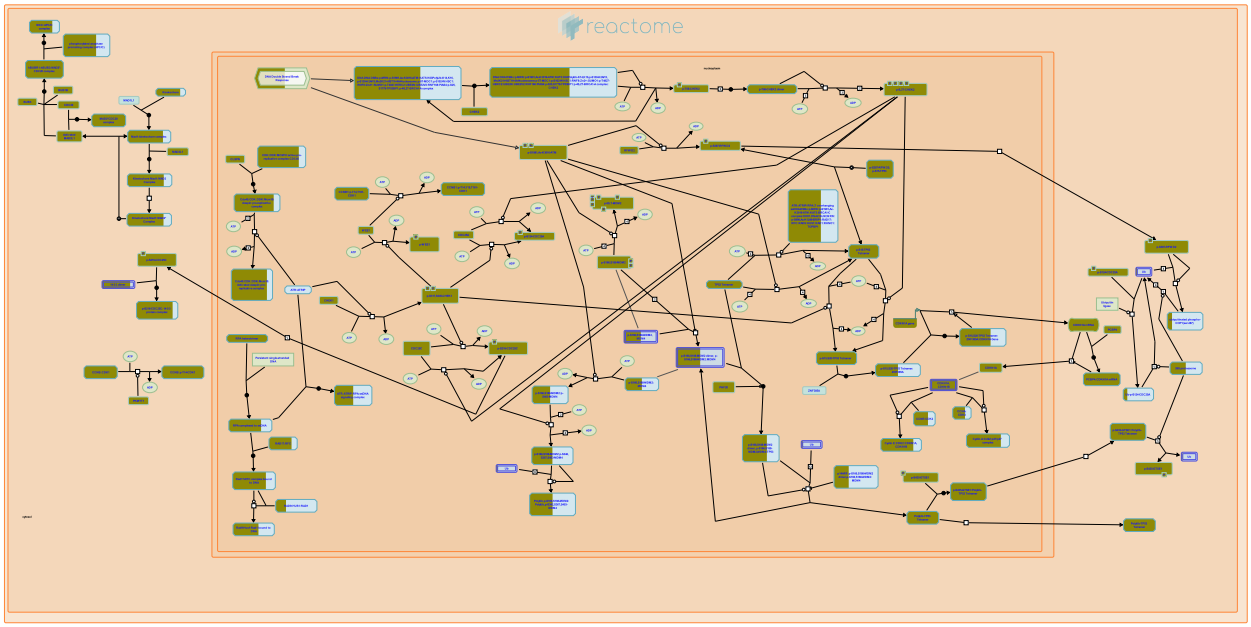
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Analysis properties

- This is an **overrepresentation** analysis: A statistical (hypergeometric distribution) test that determines whether certain Reactome pathways are over-represented (enriched) in the submitted data. It answers the question ‘Does my list contain more proteins for pathway X than would be expected by chance?’ This test produces a probability score, which is corrected for false discovery rate using the Benjamani-Hochberg method.
  See more
- 5214 out of 8127 identifiers in the sample were found in Reactome, where 2430 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent. ↗
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAyNDA1MTYxODM0MTNfNTI4Mw%3D%3D. This ID is valid for at least 7 days in Reactome’s server. Use it to access Reactome services with your data.

Cell Cycle Checkpoints ↗

Stable identifier: R-HSA-69620



A hallmark of the human cell cycle in normal somatic cells is its precision. This remarkable fidelity is achieved by a number of signal transduction pathways, known as checkpoints, which monitor cell cycle progression ensuring an interdependency of S-phase and mitosis, the integrity of the genome and the fidelity of chromosome segregation.

Checkpoints are layers of control that act to delay CDK activation when defects in the division program occur. As the CDKs functioning at different points in the cell cycle are regulated by different means, the various checkpoints differ in the biochemical mechanisms by which they elicit their effect. However, all checkpoints share a common hierarchy of a sensor, signal transducers, and effectors that interact with the CDKs.

The stability of the genome in somatic cells contrasts to the almost universal genomic instability of tumor cells. There are a number of documented genetic lesions in checkpoint genes, or in cell cycle genes themselves, which result either directly in cancer or in a predisposition to certain cancer types. Indeed, restraint over cell cycle progression and failure to monitor genome integrity are likely prerequisites for the molecular evolution required for the development of a tumor. Perhaps most notable amongst these is the p53 tumor suppressor gene, which is mutated in >50% of human tumors. Thus, the importance of the checkpoint pathways to human biology is clear.

Editions

2005-01-01	Authored	O'Donnell, M., Walworth, N., Hoffmann, I., Khanna, KK., Yen, TJ.
2013-11-25	Edited	Matthews, L.
2024-03-06	Reviewed	Sanchez, Y., Knudsen, E., Hardwick, KG.

200 submitted entities found in this pathway, mapping to 215 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AMFR	O76064	ANAPC1	Q9H1A4	ANAPC10	Q9UM13
ANAPC16	Q96DE5	ANAPC2	Q9UJX6	ANAPC7	Q9UJX3
ATM	Q13315	AURKB	Q96GD4	B9D2	Q9BPU9
BABAM2	Q9NXR7	BACH1	Q9BX63	BARD1	Q99728
BIRC5	O15392	BLM	P54132	BRCA1	P38398
BRIP1	Q9BX63	BUB1	O43683, O60566	BUB1B	O60566
BUB3	O43684	CCN1	P20248	CCNA2	P20248
CCNB1	P14635	CCNB2	O95067	CCNE2	O96020
CCNL1	P49736	CDC16	Q13042	CDC20	Q12834
CDC23	Q9UJX2	CDC25A	P30304	CDC25C	P30307

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CDC27	P30260	CDC45	O75419	CDC6	Q99741
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CDK2	P24941	CDKN1A	P38936	CDKN1B	P46527
CENPA	P49450	CENPE	Q02224	CENPF	P49454
CENPH	Q9H3R5	CENPI	Q92674	CENPK	Q9BS16
CENPL	Q8N0S6	CENPM	Q9NSP4	CENPN	Q96H22
CENPO	Q9BU64	CENPP	Q6IPU0	CENPQ	Q7L2Z9
CENPT	Q96BT3	CENPU	Q71F23	CHEK1	O14757
CHEK2	O96017	CKAP5	Q14008	CLASP1	Q7Z460
CLASP2	O75122	CLIP1	P30622	CLSPN	Q9HAW4
COP1	Q8NHY2	DBF4	Q9UBU7	DLC1	P63167
DSN1	Q9H410	DYNC1H1	Q14204	DYNC1I1	O14576
DYNC1I2	Q13409	DYNC1LI1	Q9Y6G9	DYNLL1	P63167
DYNLL2	Q96FJ2	EMB	O14980	ERCC6L	Q2NKX8
EXO1	Q9UQ84	FUNDC2	P46736	GTSE1	Q9NYZ3
H2AX	P16104	H2BC11	P06899	H2BC21	P06899, Q16778
H2BC5	P58876, Q93079, Q99879	H2BC8	P62807, Q99879	H2BC9	P58876, Q93079
H4C8	P62805	HERC2	O95714	HUS1	O60921
INCENP	Q9NQS7	ITGB3BP	Q13352	KIF18A	Q8NI77
KIF2A	O00139	KIF2C	Q99661	KNL1	Q8NG31
KNTC1	P50748	MAD2L1	Q13257	MAPRE1	Q15691
MCM10	Q7L590	MCM2	P33993, P49736	MCM3	P25205
MCM4	P33991	MCM5	P33992	MCM6	Q14566
MCM7	P33993	MCM8	Q9UJA3	MDC1	Q14676
MDM2	Q00987	MIS12	Q9H081	MRE11	P49959
NDC80	O14777	NDE1	Q9NXR1	NDEL1	Q9GZM8
NSD2	O96028	NSL1	Q96IY1	NUDC	Q9Y266
NUF2	Q9BZD4	NUP107	P57740	NUP37	Q8NFH4
NUP43	Q8NFH3	NUP85	Q9BW27	ORC1	Q13415
ORC3	Q9UBD5	ORC4	O43929	ORC5	O43913
ORC6	Q9Y5N6	PCBP4	P57723	PHF20	Q9BVI0
PIAS4	Q8N2W9	PKMYT1	Q99640	PLK1	P53350
PPP1CC	P36873	PPP2CA	P67775	PPP2CB	P62714
PPP2R1A	P30153	PPP2R1B	P30154	PPP2R5D	Q14738
PSMA4	P25789	PSMB10	P40306, Q99436	PSMB6	P28072
PSMB7	P40306, Q99436	PSMB8	P28062	PSMC1	P62191
PSMC2	P35998	PSMC3	P17980	PSMD1	Q99460
PSMD10	O75832	PSMD11	O00231	PSMD13	Q9UNM6
PSMD14	O00487	PSMD2	Q13200	PSMD3	O43242
PSMD4	P55036	PSMD5	Q16401	PSMD6	Q15008
PSMD8	P48556	PSME1	Q06323	PSMF1	Q92530
RAD50	Q92878	RANBP2	P49792	RANGAP1	P46060
RBBP8	Q99708	RCC2	Q9P258	RFC2	P35250
RFC3	P40937, P40938	RFC4	P35249	RFC5	P40937, P40938
RHNO1	Q9BSD3	RMI1	Q9H9A7	RMI2	Q96E14
RNF168	Q8IYW5	RPA1	P27694	RPA2	P15927
RPA3	P35244	RPN1	Q13200	RPS27A	P62979
SEC13	P55735	SEH1L	Q96EE3-1	SEM1	P60896

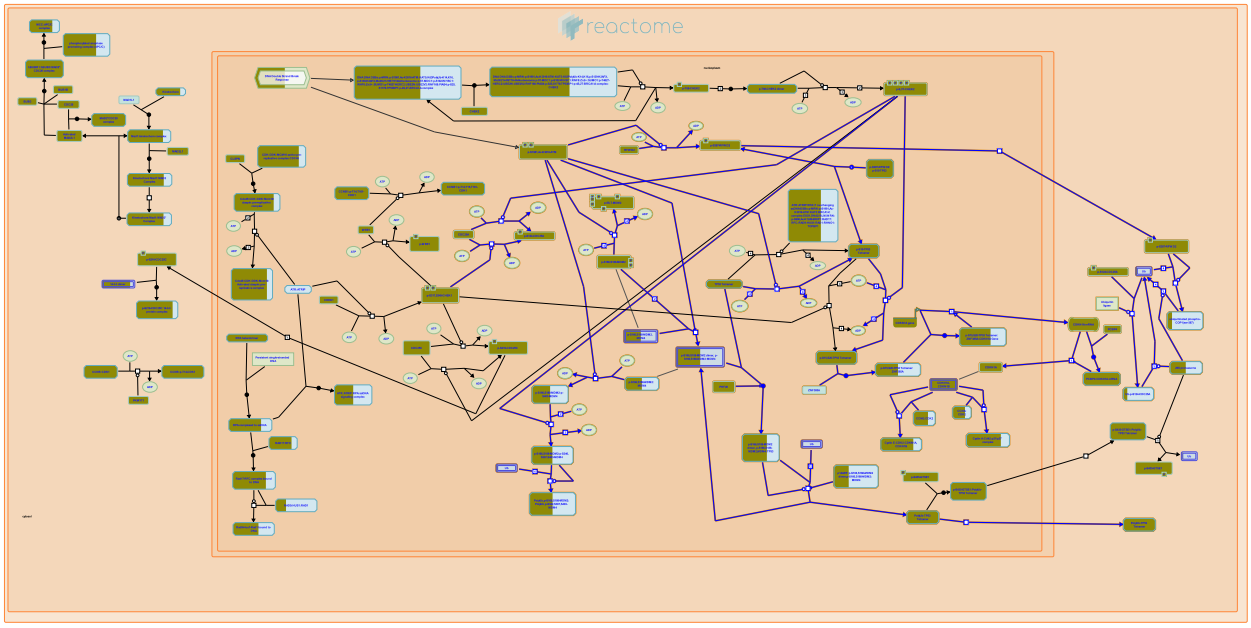
Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
SGO1	Q5FBB7	SGO2	Q562F6	SKA1	Q96BD8
SKA2	Q8WVK7	SPC24	Q8NBT2	SPC25	Q9HBM1
SPDL1	Q96EA4	TAOK1	Q7L7X3	TOPBP1	Q92547
TP53	P04637	TP53BP1	Q12888	UBE2C	O00762
UBE2D1	P51668	UBE2E1	P51965	UBE2N	P61088
UBE2S	Q16763	UIMC1	Q96RL1	WEE1	P30291
XPO1	O14980	YWHAE	P62258	YWHAG	P61981
YWHAH	Q04917	YWHAQ	P27348, P31947	YWHAZ	P27348, P63104
ZWILCH	Q9H900	ZWINT	O95229		

Input	Ensembl Id
CDKN1A	ENSG00000124762, ENST00000244741

G1/S DNA Damage Checkpoints ↗

Location: Cell Cycle Checkpoints

Stable identifier: R-HSA-69615



In the G1 phase there are two types of DNA damage responses, the p53-dependent and the p53-independent pathways. The p53-dependent responses inhibit CDKs through the up-regulation of genes encoding CKIs mediated by the p53 protein, whereas the p53-independent mechanisms inhibit CDKs through the inhibitory T14Y15 phosphorylation of Cdk2. Failure of DNA damage checkpoints in G1 leads to mutagenic replication of damaged templates and other replication defects.

Editions

2003-06-05	Authored	Hoffmann, I., Khanna, KK.

39 submitted entities found in this pathway, mapping to 43 Reactome entities

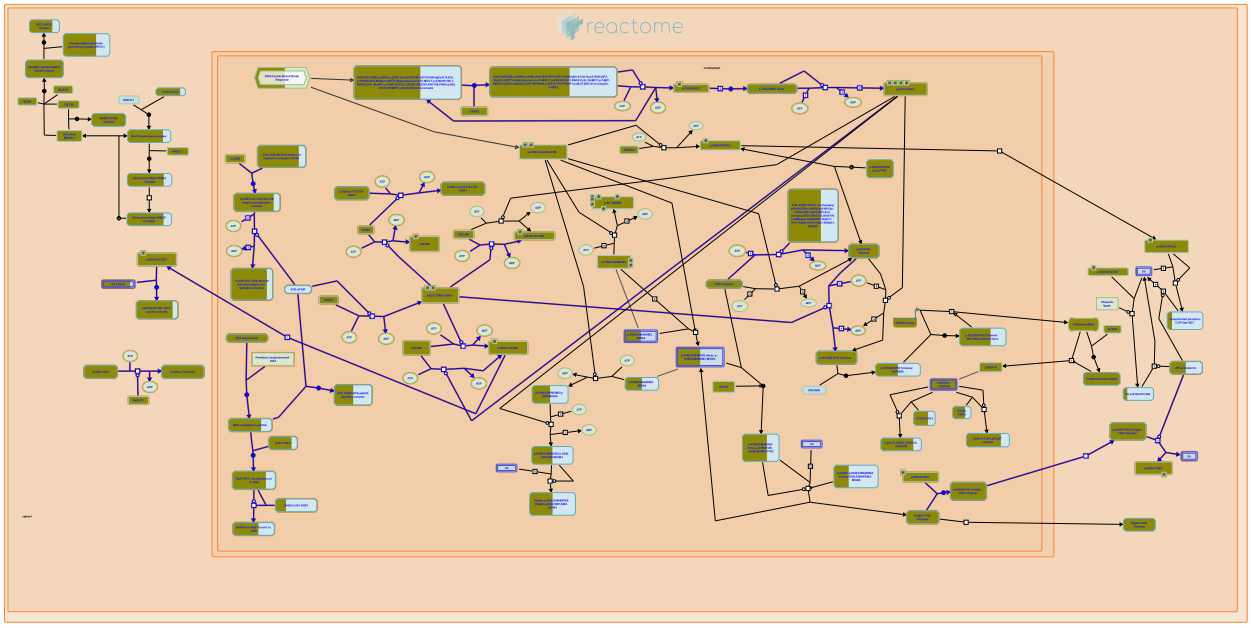
Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ATM	Q13315	CCN1	P20248	CCNA2	P20248
CCNE2	O96020	CDC25A	P30304	CDK2	P24941
CDKN1A	P38936	CDKN1B	P46527	CHEK1	O14757
CHEK2	O96017	COP1	Q8NHY2	MDM2	Q00987
PCBP4	P57723	PHF20	Q9BVI0	PSMA4	P25789
PSMB10	P40306, Q99436	PSMB6	P28072	PSMB7	P40306, Q99436
PSMB8	P28062	PSMC1	P62191	PSMC2	P35998
PSMC3	P17980	PSMD1	Q99460	PSMD10	O75832
PSMD11	O00231	PSMD13	Q9UNM6	PSMD14	O00487
PSMD2	Q13200	PSMD3	O43242	PSMD4	P55036
PSMD5	Q16401	PSMD6	Q15008	PSMD8	P48556
PSME1	Q06323	PSMF1	Q92530	RPN1	Q13200
RPS27A	P62979	SEM1	P60896	TP53	P04637

Input	Ensembl Id
CDKN1A	ENSG00000124762, ENST00000244741

G2/M Checkpoints ↗

Location: Cell Cycle Checkpoints

Stable identifier: R-HSA-69481



G2/M checkpoints include the checks for damaged DNA, unreplicated DNA, and checks that ensure that the genome is replicated once and only once per cell cycle. If cells pass these checkpoints, they follow normal transition to the M phase. However, if any of these checkpoints fail, mitotic entry is prevented by specific G2/M checkpoint events.

The G2/M checkpoints can fail due to the presence of unreplicated DNA or damaged DNA. In such instances, the cyclin-dependent kinase, Cdc2(Cdk1), is maintained in its inactive, phosphorylated state, and mitotic entry is prevented. Events that ensure that origins of DNA replication fire once and only once per cell cycle are also an example of a G2/M checkpoint.

In the event of high levels of DNA damage, the cells may also be directed to undergo apopotosis (not covered).

100 submitted entities found in this pathway, mapping to 112 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AMFR	O76064	ATM	Q13315	BABAM2	Q9NXR7
BACH1	Q9BX63	BARD1	Q99728	BLM	P54132
BRCA1	P38398	BRIP1	Q9BX63	CCNB1	P14635
CCNB2	O95067	CCNL1	P49736	CDC25A	P30304
CDC25C	P30307	CDC45	O75419	CDC6	Q99741
CDC7	O00311	CDK1	P06493	CDK2	P24941
CHEK1	O14757	CHEK2	O96017	CLSPN	Q9HAW4
DBF4	Q9UBU7	EXO1	Q9UQ84	FUNDC2	P46736
GTSE1	Q9NYZ3	H2AX	P16104	H2BC11	P06899
H2BC21	P06899, Q16778	H2BC5	P58876, Q93079, Q99879	H2BC8	P62807, Q99879
H2BC9	P58876, Q93079	H4C8	P62805	HERC2	O95714
HUS1	O60921	MCM10	Q7L590	MCM2	P33993, P49736
MCM3	P25205	MCM4	P33991	MCM5	P33992
MCM6	Q14566	MCM7	P33993	MCM8	Q9UJA3
MDC1	Q14676	MRE11	P49959	NSD2	O96028
ORC1	Q13415	ORC3	Q9UBD5	ORC4	O43929
ORC5	O43913	ORC6	Q9Y5N6	PIAS4	Q8N2W9

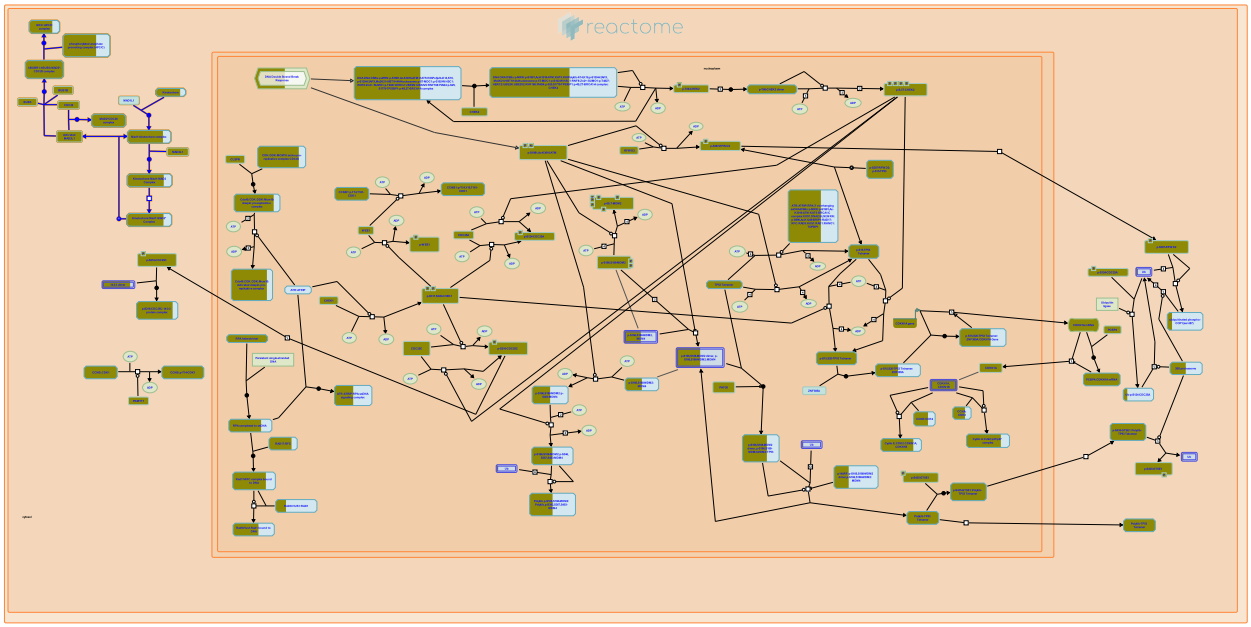
Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
PKMYT1	Q99640	PSMA4	P25789	PSMB10	P40306, Q99436
PSMB6	P28072	PSMB7	P40306, Q99436	PSMB8	P28062
PSMC1	P62191	PSMC2	P35998	PSMC3	P17980
PSMD1	Q99460	PSMD10	O75832	PSMD11	O00231
PSMD13	Q9UNM6	PSMD14	O00487	PSMD2	Q13200
PSMD3	O43242	PSMD4	P55036	PSMD5	Q16401
PSMD6	Q15008	PSMD8	P48556	PSME1	Q06323
PSMF1	Q92530	RAD50	Q92878	RBBP8	Q99708
RFC2	P35250	RFC3	P40937, P40938	RFC4	P35249
RFC5	P40937, P40938	RHNO1	Q9BSD3	RMI1	Q9H9A7
RMI2	Q96E14	RNF168	Q8IYW5	RPA1	P27694
RPA2	P15927	RPA3	P35244	RPN1	Q13200
RPS27A	P62979	SEM1	P60896	TOPBP1	Q92547
TP53	P04637	TP53BP1	Q12888	UBE2N	P61088
UIMC1	Q96RL1	WEE1	P30291	YWHAE	P62258
YWHAG	P61981	YWHAH	Q04917	YWHAQ	P27348, P31947
YWHAZ	P27348, P63104				

Mitotic Spindle Checkpoint ↗

Location: Cell Cycle Checkpoints

Stable identifier: R-HSA-69618

Compartments: cytosol



The mitotic checkpoint or spindle assembly checkpoint is an evolutionarily conserved mechanism that ensures that cells with misaligned chromosomes do not exit mitosis and divide to form aneuploid cells. As chromosome attachment to the spindle microtubules is a stochastic process, not all chromosomes achieve alignment at the spindle equator at the same time. It is therefore essential that even a single unaligned chromosome can prevent the onset of anaphase. The ability of the checkpoint to monitor the status of chromosome alignment is achieved by assigning checkpoint proteins to the kinetochore, a macromolecular complex that resides at centromeres of chromosomes that establishes connections with spindle microtubules.

The checkpoint proteins monitor, in an unknown way, the mechanical activities between kinetochore-associated proteins and microtubules. Defects in mechanical activities at kinetochores activate the resident checkpoint proteins to initiate a signal that is amplified throughout the cell that ultimately prevents the activation of the proteolytic process that is required for sister chromatid separation and the onset of anaphase. Kinetochores of unaligned chromosomes differ from those of aligned chromosomes in two ways. Kinetochores of aligned chromosomes are saturated with between 20 to 30 microtubules. In addition, poleward directed forces exerted at each sister kinetochore generates tension between them. Unaligned kinetochores on the other hand, are not saturated with microtubules and are not under tension. The mitotic checkpoint detects the presence of unattached kinetochores rather than monitoring for the presence of attached kinetochores. Consequently, unattached kinetochores emit an inhibitory signal that inhibits the biochemical events that are required to initiate the onset of anaphase. The mechanism by which this inhibitory signal is generated at unattached kinetochores has not precisely been determined but the signal is generated as a result of the lack of microtubule occupancy and kinetochore tension. A single unattached kinetochore is capable of preventing cells from exiting mitosis. The mitotic checkpoint provides a way for a localized defect to affect the global biochemical status of the cell. In principle, the signal that is generated at an unattached kinetochore diffuses throughout the cell to affect its target. There are currently two models for how this is achieved. One model is based on the observation that the Mad2 checkpoint protein binds and is rapidly released from unattached kinetochores. The kinetochore is believed to act as a catalyst that converts Mad2 into an inhibitory state that diffuses throughout the cell upon its release from the kinetochore. A second model proposes that the signal is amplified by a kinase cascade much like a conventional signal transduction pathway. This kinase cascade is believed to be comprised of the checkpoint kinases, hBUBR1, hBUB1, hMPS1.

Literature references

Yen, TJ., Chan, GK. (2003). The mitotic checkpoint: a signaling pathway that allows a single unattached kinetochore to inhibit mitotic exit. *Prog Cell Cycle Res, 5*, 431-9. ↗

Hardwick, KG., Musacchio, A. (2002). The spindle checkpoint: structural insights into dynamic signalling. *Nat Rev Mol Cell Biol, 3*, 731-41. ↗

Editions

2004-05-05	Authored	Yen, TJ.

91 submitted entities found in this pathway, mapping to 92 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ANAPC1	Q9H1A4	ANAPC10	Q9UM13	ANAPC16	Q96DE5
ANAPC2	Q9UJX6	ANAPC7	Q9UJX3	AURKB	Q96GD4
B9D2	Q9BPU9	BIRC5	O15392	BUB1	O43683, O60566
BUB1B	O60566	BUB3	O43684	CDC16	Q13042
CDC20	Q12834	CDC23	Q9UJX2	CDC27	P30260
CDCA8	Q53HL2	CENPA	P49450	CENPE	Q02224
CENPF	P49454	CENPH	Q9H3R5	CENPI	Q92674
CENPK	Q9BS16	CENPL	Q8N0S6	CENPM	Q9NSP4
CENPN	Q96H22	CENPO	Q9BU64	CENPP	Q6IPU0
CENPQ	Q7L2Z9	CENPT	Q96BT3	CENPU	Q71F23
CKAP5	Q14008	CLASP1	Q7Z460	CLASP2	O75122
CLIP1	P30622	DLC1	P63167	DSN1	Q9H410
DYNC1H1	Q14204	DYNC1I1	O14576	DYNC1I2	Q13409
DYNC1LI1	Q9Y6G9	DYNLL1	P63167	DYNLL2	Q96FJ2
EMB	O14980	ERCC6L	Q2NKX8	INCENP	Q9NQS7
ITGB3BP	Q13352	KIF18A	Q8NI77	KIF2A	O00139
KIF2C	Q99661	KNL1	Q8NG31	KNTC1	P50748
MAD2L1	Q13257	MAPRE1	Q15691	MIS12	Q9H081
NDC80	O14777	NDE1	Q9NXR1	NDEL1	Q9GZM8
NSL1	Q96IY1	NUDC	Q9Y266	NUF2	Q9BZD4
NUP107	P57740	NUP37	Q8NFH4	NUP43	Q8NFH3
NUP85	Q9BW27	PLK1	P53350	PPP1CC	P36873
PPP2CA	P67775	PPP2CB	P62714	PPP2R1A	P30153
PPP2R1B	P30154	PPP2R5D	Q14738	RANBP2	P49792
RANGAP1	P46060	RCC2	Q9P258	SEC13	P55735
SEH1L	Q96EE3-1	SGO1	Q5FBB7	SGO2	Q562F6
SKA1	Q96BD8	SKA2	Q8WVK7	SPC24	Q8NBT2
SPC25	Q9HBM1	SPDL1	Q96EA4	TAOK1	Q7L7X3
UBE2C	O00762	UBE2D1	P51668	UBE2E1	P51965
UBE2S	Q16763	XPO1	O14980	ZWILCH	Q9H900
ZWINT	O95229				

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