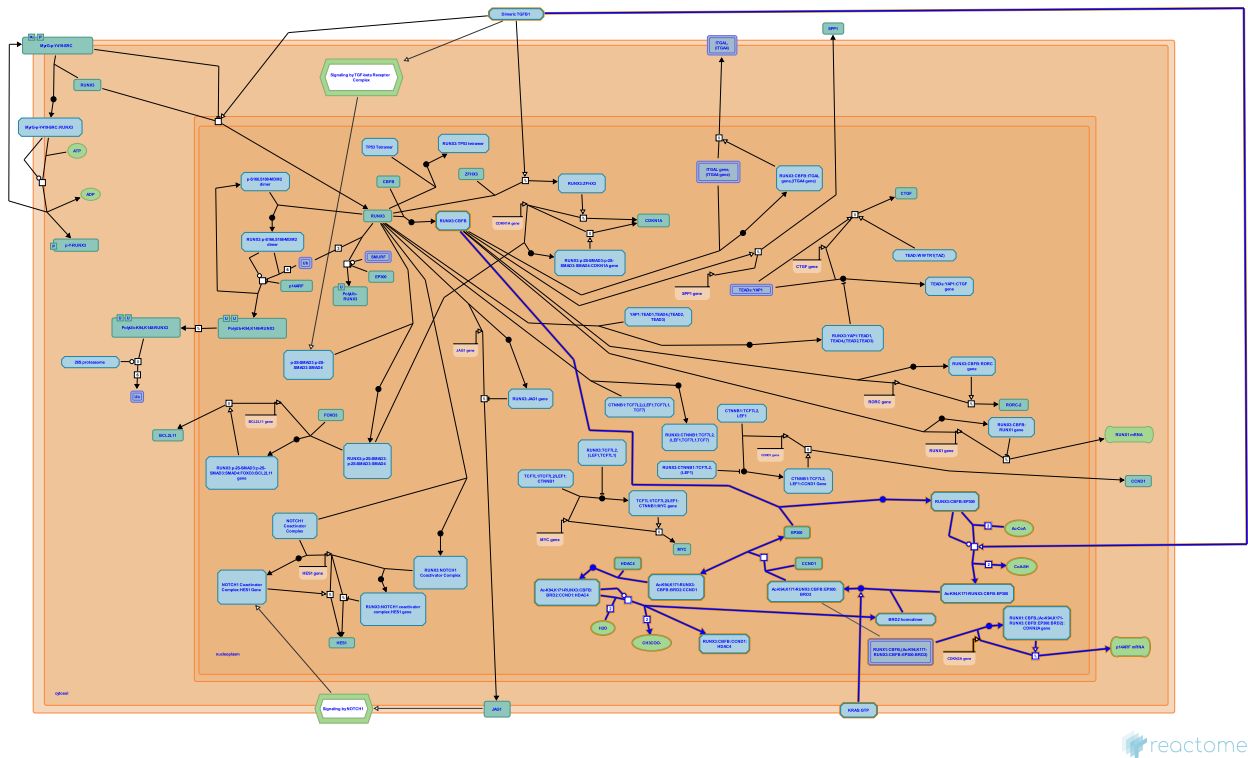


# RUNX3 regulates p14-ARF



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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](https://reactome.org/textbook/).

29/04/2024

## 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

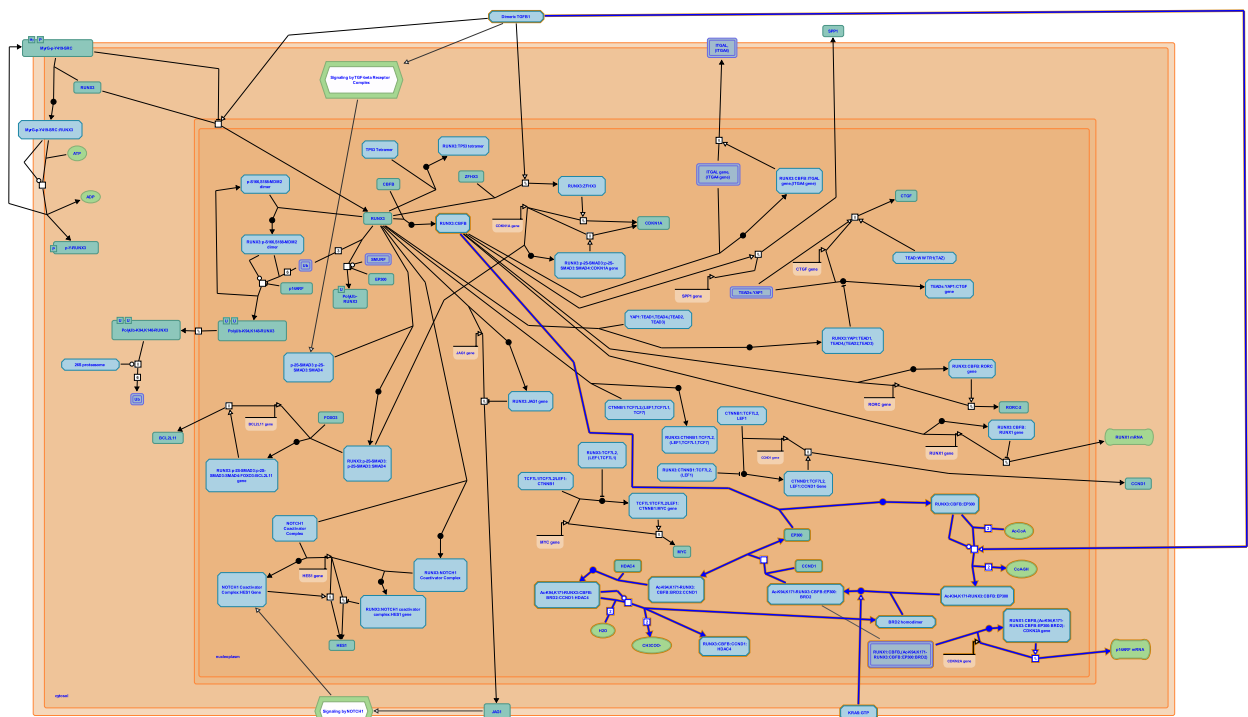
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- Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res*, 46, D649-D655. [↗](#)
- Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

Reactome database release: 88

This document contains 1 pathway and 8 reactions ([see Table of Contents](#))

# RUNX3 regulates p14-ARF ↗

Stable identifier: R-HSA-8951936



Acetylation of RUNX3 by the histone acetyl transferase p300 (EP300) and the subsequent association of acetylated RUNX3 with BRD2 correlates with upregulation of p14-ARF transcription from the CDKN2A locus. Cyclin D1 (CCND1) negatively regulates RUNX3-facilitated induction of p14-ARF by recruiting histone deacetylase HDAC4 to RUNX3, leading to RUNX3 deacetylation (Lee et al. 2013).

## Literature references

Lee, JW., Lee, YS., Chuang, LS., Kim, JH., Bae, SC., Jang, JW. et al. (2013). Runx3 inactivation is a crucial early event in the development of lung adenocarcinoma. *Cancer Cell*, 24, 603-16. ↗

## Editions

2016-12-13	Authored	Orlic-Milacic, M.
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2017-01-31	Edited	Orlic-Milacic, M.

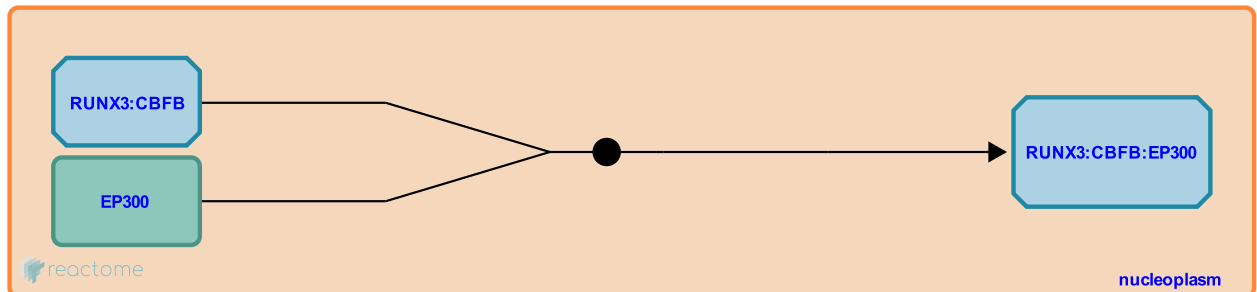
## RUNX3 binds EP300 [↗](#)

**Location:** [RUNX3 regulates p14-ARF](#)

**Stable identifier:** R-HSA-8951951

**Type:** binding

**Compartments:** nucleoplasm



The histone acetyltransferase EP300 (p300) forms a complex with RUNX3, presumably bound to CBFB (Jin et al. 2004, Lee et al. 2013). EP300 can also form a complex with other RUNX family members, RUNX1 and RUNX2 (Jin et al. 2004).

**Followed by:** [EP300 acetylates RUNX3](#)

## Literature references

Lee, JW., Lee, YS., Chuang, LS., Kim, JH., Bae, SC., Jang, JW. et al. (2013). Runx3 inactivation is a crucial early event in the development of lung adenocarcinoma. *Cancer Cell*, 24, 603-16. [↗](#)

Jeon, EJ., Jin, YH., Lee, YH., Li, QL., Lee, KY., Bae, SC. et al. (2004). Transforming growth factor-beta stimulates p300-dependent RUNX3 acetylation, which inhibits ubiquitination-mediated degradation. *J. Biol. Chem.*, 279, 29409-17. [↗](#)

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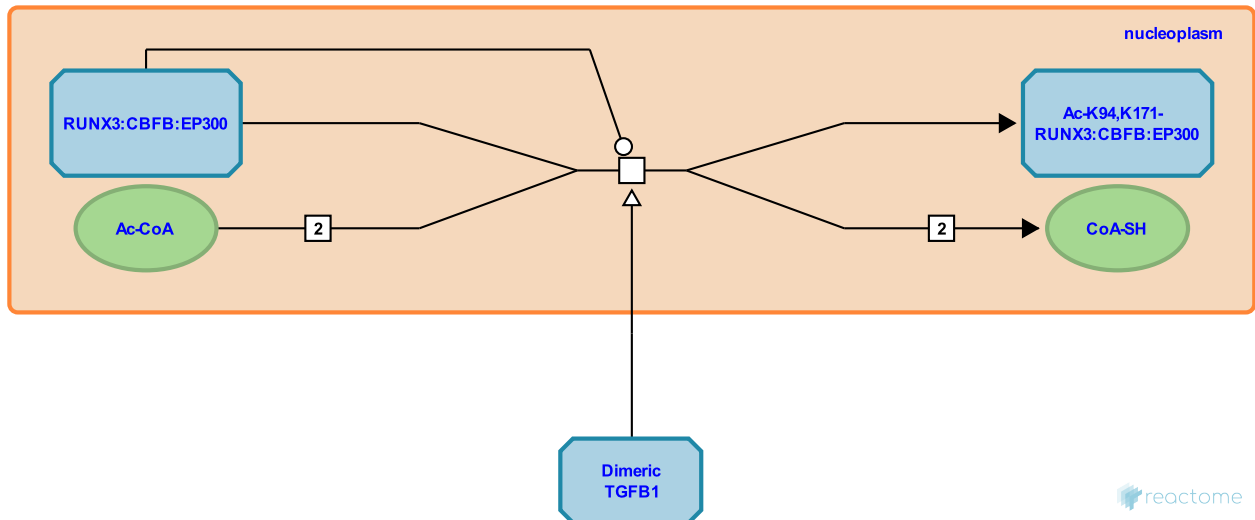
## EP300 acetylates RUNX3 [↗](#)

**Location:** [RUNX3 regulates p14-ARF](#)

**Stable identifier:** R-HSA-8951966

**Type:** transition

**Compartments:** nucleoplasm



EP300 (p300) histone acetyltransferase acetylates RUNX3 on lysine residues K94 and K171 (Lee et al. 2013), and probably other lysines (Jin et al. 2004). EP300-mediated acetylation of RUNX3 is positively regulated by TGF-beta treatment. Besides increasing the transcriptional activity of RUNX3, EP300-mediated acetylation also increases the half-life of RUNX3, as it interferes with SMURF-mediated ubiquitination and subsequent degradation of RUNX3 (Jin et al. 2004).

**Preceded by:** [RUNX3 binds EP300](#)

**Followed by:** [Acetylated RUNX3 binds to BRD2](#)

## Literature references

Lee, JW., Lee, YS., Chuang, LS., Kim, JH., Bae, SC., Jang, JW. et al. (2013). Runx3 inactivation is a crucial early event in the development of lung adenocarcinoma. *Cancer Cell*, 24, 603-16. [↗](#)

Jeon, EJ., Jin, YH., Lee, YH., Li, QL., Lee, KY., Bae, SC. et al. (2004). Transforming growth factor-beta stimulates p300-dependent RUNX3 acetylation, which inhibits ubiquitination-mediated degradation. *J. Biol. Chem.*, 279, 29409-17. [↗](#)

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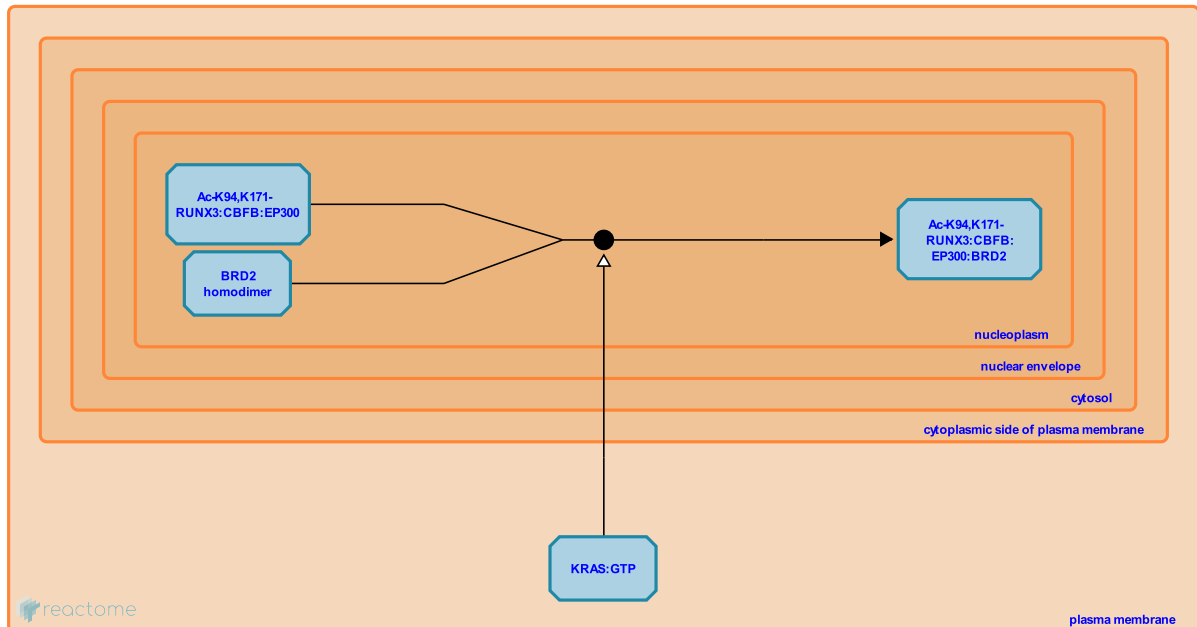
## Acetylated RUNX3 binds to BRD2 [↗](#)

**Location:** [RUNX3 regulates p14-ARF](#)

**Stable identifier:** R-HSA-8951977

**Type:** binding

**Compartments:** nucleoplasm



RUNX3 acetylated on lysine residues K94 and K171 binds to BRD2 (bromodomain-containing protein 2). Formation of the RUNX3 complex with BRD2 is stimulated by activated KRAS (Lee et al. 2013).

**Preceded by:** [EP300 acetylates RUNX3](#)

**Followed by:** [RUNX proteins bind the p14-ARF promoter at the CDKN2A locus](#), [CCND1 binds RUNX3 and displaces EP300](#)

### Literature references

Lee, JW., Lee, YS., Chuang, LS., Kim, JH., Bae, SC., Jang, JW. et al. (2013). Runx3 inactivation is a crucial early event in the development of lung adenocarcinoma. *Cancer Cell*, 24, 603-16. [↗](#)

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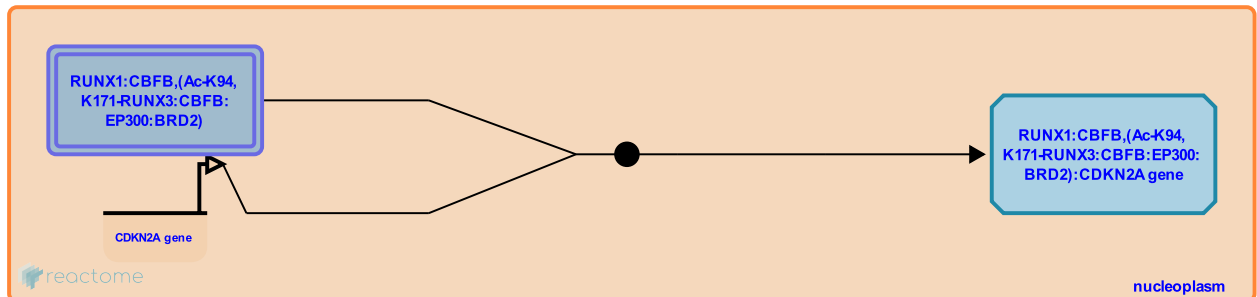
## RUNX proteins bind the p14-ARF promoter at the CDKN2A locus [↗](#)

**Location:** [RUNX3 regulates p14-ARF](#)

**Stable identifier:** R-HSA-8952081

**Type:** binding

**Compartments:** nucleoplasm



The CDKN2A gene promoter that regulates transcription of p14-ARF contains Runx response elements that are known to be recognized by the RUNX1:CBFB complex (Linggi et al. 2002). Based on sequence similarity between RUNX1 and RUNX3 and the fact that the complex of acetylated RUNX3 and BRD2 positively regulate p14-ARF transcription, it is possible that RUNX3 can also bind to the Runx response elements at the p14-ARF promoter (Lee et al. 2013).

**Preceded by:** [Acetylated RUNX3 binds to BRD2](#)

**Followed by:** [p14-ARF transcription is stimulated by RUNX proteins](#)

### Literature references

Lee, JW., Lee, YS., Chuang, LS., Kim, JH., Bae, SC., Jang, JW. et al. (2013). Runx3 inactivation is a crucial early event in the development of lung adenocarcinoma. *Cancer Cell*, 24, 603-16. [↗](#)

Berdel, WE., Serve, H., Nip, J., van der Reijden, B., Linggi, B., Hiebert, SW. et al. (2002). The t(8;21) fusion protein, AML1 ETO, specifically represses the transcription of the p14(ARF) tumor suppressor in acute myeloid leukemia. *Nat. Med.*, 8, 743-50. [↗](#)

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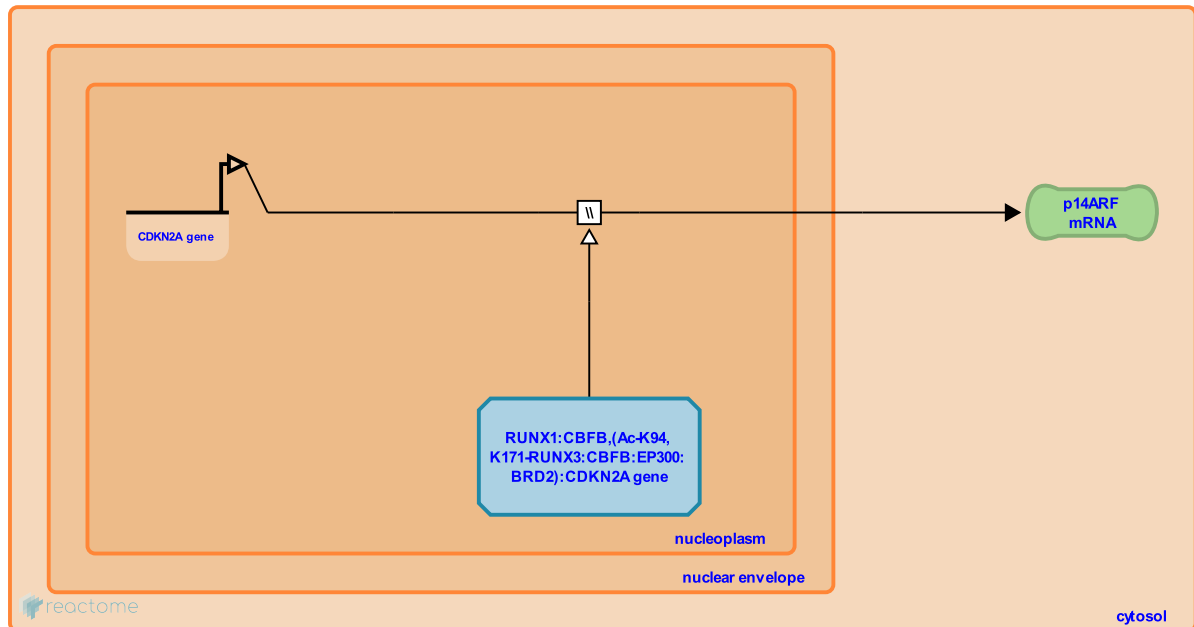
## p14-ARF transcription is stimulated by RUNX proteins ↗

**Location:** [RUNX3 regulates p14-ARF](#)

**Stable identifier:** R-HSA-8952101

**Type:** omitted

**Compartments:** nucleoplasm, cytosol



Binding of the RUNX1:CBFB complex to the p14-ARF promoter at the CDKN2A locus promotes p14-ARF transcription (Linggi et al. 2002). The complex of acetylated RUNX3 and BRD2 positively regulates p14-ARF transcription, leading to activation of TP53 (p53) in response to oncogenic KRAS signaling. It is possible that RUNX3 directly binds to Runx response elements in the p14-ARF promoter that are recognized by RUNX1, although the direct association of RUNX3 with the CDKN2A gene has not been examined (Lee et al. 2013).

**Preceded by:** [RUNX proteins bind the p14-ARF promoter at the CDKN2A locus](#)

### Literature references

Lee, JW., Lee, YS., Chuang, LS., Kim, JH., Bae, SC., Jang, JW. et al. (2013). Runx3 inactivation is a crucial early event in the development of lung adenocarcinoma. *Cancer Cell*, 24, 603-16. ↗

Berdel, WE., Serve, H., Nip, J., van der Reijden, B., Linggi, B., Hiebert, SW. et al. (2002). The t(8;21) fusion protein, AML1 ETO, specifically represses the transcription of the p14(ARF) tumor suppressor in acute myeloid leukemia. *Nat. Med.*, 8, 743-50. ↗

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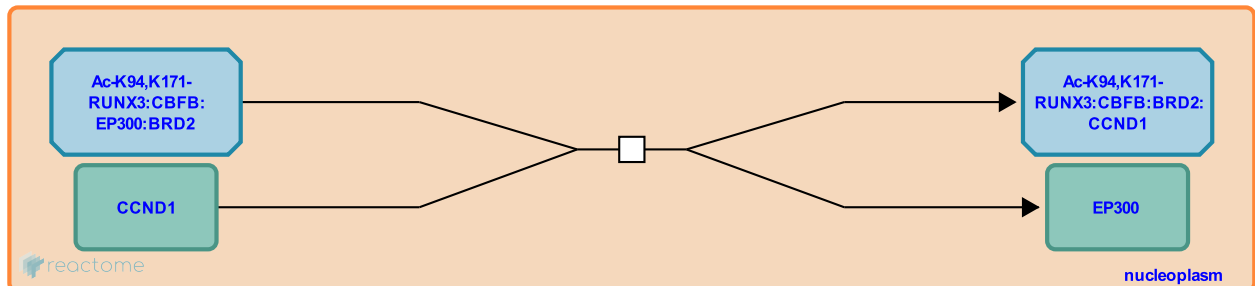
## CCND1 binds RUNX3 and displaces EP300 [↗](#)

**Location:** [RUNX3 regulates p14-ARF](#)

**Stable identifier:** R-HSA-8952058

**Type:** transition

**Compartments:** nucleoplasm



CCND1 (cyclin D1) can bind to RUNX3 and displace EP300 (p300) histone acetyltransferase (Lee et al. 2013).

**Preceded by:** [Acetylated RUNX3 binds to BRD2](#)

**Followed by:** [CCND1 recruits HDAC4 to RUNX3](#)

### Literature references

Lee, JW., Lee, YS., Chuang, LS., Kim, JH., Bae, SC., Jang, JW. et al. (2013). Runx3 inactivation is a crucial early event in the development of lung adenocarcinoma. *Cancer Cell*, 24, 603-16. [↗](#)

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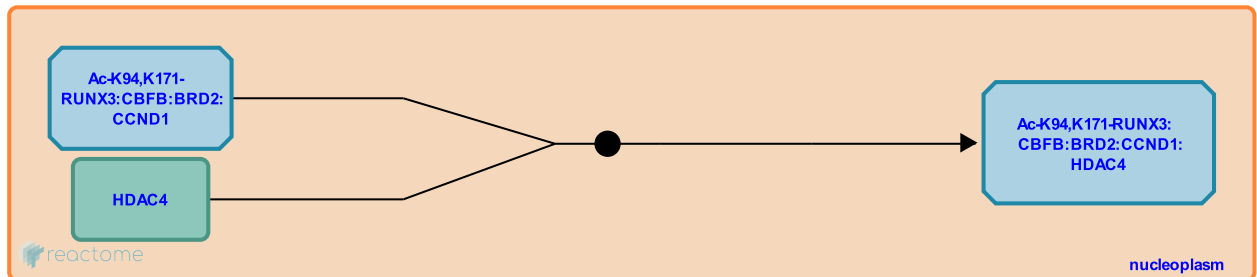
## CCND1 recruits HDAC4 to RUNX3 [↗](#)

**Location:** [RUNX3 regulates p14-ARF](#)

**Stable identifier:** R-HSA-8952062

**Type:** binding

**Compartments:** nucleoplasm



CCND1 (cyclin D1) recruits histone deacetylase HDAC4 to acetylated RUNX3 (Lee et al. 2013).

**Preceded by:** [CCND1 binds RUNX3 and displaces EP300](#)

**Followed by:** [HDAC4 deacetylates RUNX3](#)

### Literature references

Lee, JW., Lee, YS., Chuang, LS., Kim, JH., Bae, SC., Jang, JW. et al. (2013). Runx3 inactivation is a crucial early event in the development of lung adenocarcinoma. *Cancer Cell*, 24, 603-16. [↗](#)

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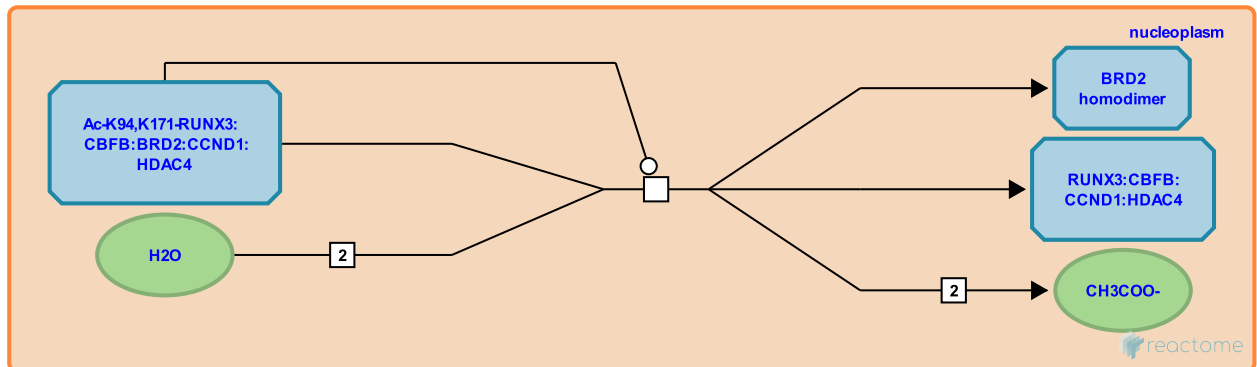
## HDAC4 deacetylates RUNX3 [↗](#)

**Location:** [RUNX3 regulates p14-ARF](#)

**Stable identifier:** R-HSA-8952069

**Type:** transition

**Compartments:** nucleoplasm



Histone deacetylase HDAC4, recruited to RUNX3 by CCND1 (cyclin D1), deacetylates RUNX3, leading to BRD2 dissociation (Lee et al. 2013).

**Preceded by:** [CCND1 recruits HDAC4 to RUNX3](#)

### Literature references

Lee, JW., Lee, YS., Chuang, LS., Kim, JH., Bae, SC., Jang, JW. et al. (2013). Runx3 inactivation is a crucial early event in the development of lung adenocarcinoma. *Cancer Cell*, 24, 603-16. [↗](#)

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