

Formation of Senescence-Associated Het-

erochromatin Foci (SAHF)



reactome

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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.

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This document contains 1 pathway and 2 reactions (see Table of Contents)

Formation of Senescence-Associated Heterochromatin Foci (SAHF) 7

Stable identifier: R-HSA-2559584



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The process of DNA damage/telomere stress induced senescence culminates in the formation of senescence associated heterochromatin foci (SAHF). These foci represent facultative heterochromatin that is formed in senescent cells. They contribute to the repression of proliferation promoting genes and play an important role in the permanent cell cycle exit that characterizes senescence (Narita et al. 2003 and 2006). SAHF appear as compacted, punctate DAPI stained foci of DNA. Each chromosome is condensed into a single SAH focus, with telomeric and centromeric chromatin located predominantly at its periphery (Funayama et al. 2006, Zhang et al. 2007).

An evolutionarily conserved protein complex of HIRA, ASF1A, UBN1 and CABIN1 plays a crucial role in the SAHF formation. As cells approach senescence, HIRA, ASF1A, UBN1 and CABIN1 accumulate at the PML bodies (Zhang et al. 2005, Banumathy et al. 2009, Rai et al. 2011). PML bodies are punctate nuclear structures that contain PML protein and numerous other proteins and are proposed to be the sites of assembly of macromolecular regulatory complexes and protein modification (Fogal et al. 2000, Guo et al. 2000, Pearson et al. 2000). Recruitment of HIRA to PML bodies coincides with altered chromatin structure and deposition of macroH2A histone H2A variant onto chromatin. As cells become senescent, HIRA, ASF1A, UBN1 and CABIN1 relocate from PML bodies to SAHF. HIRA accumulation at PML bodies is RB1 and TP53 independent, but may require phosphorylation of HIRA serine S697 by GSK3B (Ye, Zerlanko, Kennedy et al. 2007). SAHF formation itself, however, requires functional RB1 and TP53 pathways (Ye, Zerlanko, Zhang et al. 2007).

SAHF contain H3K9Me mark, characteristic of trancriptionally silent chromatin, and HP1, marcoH2A histone H2A variant and HMGA proteins are also components of SAHF (Narita et al. 2006), besides the HIRA:ASF1A:UBN1:CABIN1 complex. A yet unidentified H3K9Me histone methyltransferase may be recruited to SAHF by UBN1 (Banumathy et al. 2009). One of the functions of the HIRA:ASF1A:UBN1:CABIN1 complex is to deposit histone H3.3. variant to chromatin, which influences gene expression (Zhang et al. 2007, Rai et al. 2011).

Further studies are needed to fully elucidate the mechanism of SAHF formation and mechanism by which SAHF promote cell senescence.

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Initiation of SAHF formation 7

Location: Formation of Senescence-Associated Heterochromatin Foci (SAHF)

Stable identifier: R-HSA-3878123

Type: binding

Compartments: nucleoplasm



The evolutionarily conserved complex of HIRA, ASF1A, UBN1 and CABIN1 plays a key role in the formation of senescence-associated heterochromatin foci (SAHF) (Zhang et al. 2005, Banumathy et al. 2009, Rai et al. 2011). Components of this complex, along with other proteins involved in SAHF, accumulate in PML bodies of presenescent cells, and relocate to SAHF in senescent cells, with SAHF relocation depending on the functional RB1 and TP53 pathways (Zhang et al. 2005, Ye et al. 2007, Zhang et al. 2007). HIRA serves as a scaffold of HIRA:ASF1A:UBN1:CABIN1 complex, since three different HIRA protein domains interact with ASF1A, UBN1 and CABIN1 (Zhang et al. 2005, Banumathy et al. 2009, Rai et al. 2011). One of the functions of HIRA:ASF1A:UBN1:CABIN1 complex is to deposit histone H3.3 variant onto chromatin, which is dependent on the ASF1A-mediated binding of histone H3, and is involved in the modulation of gene expression in senescent cells (Zhang et al. 2011).

Followed by: SAHF formation

Literature references

- Erzberger, JP., Ye, X., Poustovoitov, MV., Adams, PD., Dunbrack, RL., Santos, HA. et al. (2005). Formation of MacroH2A-containing senescence-associated heterochromatin foci and senescence driven by ASF1a and HIRA. *Dev. Cell*, *8*, 19-30. *¬*
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SAHF formation 7

Location: Formation of Senescence-Associated Heterochromatin Foci (SAHF)

Stable identifier: R-HSA-4647594

Type: binding

Compartments: nucleoplasm



Components of the evolutionarily conserved complex of HIRA, ASF1A, UBN1 and CABIN1 accumulate in PML bodies of pre-senescent cells, and relocate to SAHF (senescence-associated heterochromatic foci) in senescent cells, with SAHF relocation depending on the functional RB1 and TP53 pathways (Zhang et al. 2005, Ye et al. 2007, Zhang et al. 2007). The reorganization of heterochromatin into SAHFs is accompanied by reduction in the amount of total and chromatin-bound lamin B1 (LMNB1), and high levels of LMNB1 interfere with SAHF formation (Sadaie et al. 2013). High-mobility group A proteins, HMGA1 and HMGA2, are enriched on chromatin of senescent cells, predominantly localizing to SAHFs, and high HMGA1 and HMGA2 levels, in cooperation with p16-INK4A, promote SAHF formation and repression of E2F target genes in senescent cells. Overexpression of CDK4 and MDM2, which are frequently co-amplified with HMGA2 in cancer cells as a part of 12q13-15 chromosomal band amplification, bypasses HMGA2 and HMGA1 induced cell cycle arrest and SAHF formation (Narita et al. 2006). The accumulation of HMGA proteins on senescent cell chromatin and SAHF formation is accompanied by the loss of the linker histone H1, probably due to a posttranslational mechanism (Funayama et al. 2006). A chromatin remodeling protein EP400 (p400), which is able to bind CDKN1A (p21) promoter and inhibit TP53-mediated activation of CDKN1A transcription, negatively regulates SAHF formation (Chan et al. 2005).

Preceded by: Initiation of SAHF formation

Literature references

- Erzberger, JP., Ye, X., Poustovoitov, MV., Adams, PD., Dunbrack, RL., Santos, HA. et al. (2005). Formation of MacroH2A-containing senescence-associated heterochromatin foci and senescence driven by ASF1a and HIRA. *Dev. Cell*, *8*, 19-30. *¬*
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Ye, X., Somaiah, N., Zhang, R., Zerlanko, B., Salomoni, P., Adams, PD. et al. (2007). Definition of pRB- and p53-dependent and -independent steps in HIRA/ASF1a-mediated formation of senescence-associated heterochromatin foci. *Mol. Cell. Biol.*, 27, 2452-65.

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Table of Contents

Introduction	
Formation of Senescence-Associated Heterochromatin Foci (SAHF)	2
➢ Initiation of SAHF formation	4
➤ SAHF formation	5
Table of Contents	7