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Chromatin remodeling, BRCA1, SAHF and cellular senescence

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Cellular senescence is a state of stable cell growth arrest. Activation of oncogenes in primary mammalian cells typically triggers cellular senescence. Oncogene-induced senescence is an important tumor suppression mechanism, driving stable growth arrest of cancer progenitor cells harboring the initial oncogenic hit. Chromatin in the nuclei of senescent human cells is often reorganized to form specialized domains of facultative heterochromatin, known as senescence-associated heterochromatin foci (SAHF).[1] SAHF contribute to senescence-associated cell growth arrest by sequestering and silencing proliferation-promoting genes such as the E2F target gene cyclin A.[1] Notably, SAHF are different from constitutive heterochromatin, such as pericentromeres, which are largely excluded from SAHF.[1]

BRCA1 has been implicated in regulating chromatin structure. For example, oncogene-induced BRCA1 chromatin dissociation is known to regulate SAHF formation during senescence.[2] Consistently, it has been demonstrated that BRCA1 causes large-scale chromatin de-condensation.[3] In contrast, BRCA1 is implicated in regulating pericentromeric heterochromatin by silencing the repetitive satellite transcripts through ubiquitination of histone H2A.[4] This suggests that BRCA1 may function to antagonize or promote heterochromatin formation in a genomic locus-specific manner.

BRCA1 interacts with BRG1 in transformed cells. BRG1 is the catalytic subunit of the SWI/SNF chromatin-remodeling complex. BRG1 is known to regulate heterochromatin structure. For example, similar to the effects of BRCA1 loss on pericentromeres, it has been previously demonstrated that BRG1 deletion results in dissolution of pericentromeric heterochromatin.[5] These findings support the notion that the BRCA1 and BRG1 complex is critical for constitutive heterochromatin structure at pericentromeres. It will be interesting to investigate whether the BRCA1 and BRG1 complex remains at pericentromeres to maintain the silencing of the satellite repeats in senescent cells.

Activation of oncogenes such as RAS dissociates BRCA1 from chromatin.[2] Interestingly, the interaction between BRCA1 and BRG1 is disrupted in cells undergoing senescence.[6] This correlates with an increase in the level of BRG1 in the chromatin fraction.[6] Indeed, ectopic BRG1 is sufficient to drive SAHF formation. Further, BRCA1 chromatin dissociation and the disruption of the interaction between BRCA1 and BRG1 correlate with SAHF formation during senescence.[6] This suggests that BRCA1 antagonizes SAHF formation in the euchromatic genomic loci that encode for proliferation-promoting genes by sequestering BRG1 away from chromatin. Consequently, dissociation of BRCA1 from chromatin silences the expression of these genes through SAHF formation by BRG1. In addition, we discovered that the association of BRG1 with the promoters of the p21- and p16-encoding genes are enhanced during senescence.[6] However, there is no detectable change in BRCA1's association with the promoters of these genes.[6] These findings suggest that BRG1 promotes or silences the expression of its target genes in a context-dependent manner during senescence. Further studies using global profiling of the changes in the distribution of BRG1 and BRCA1 by chromatin immunoprecipitation followed by next generation sequencing (ChIP-seq) in young and senescent cells will ultimately test these possibilities.

As discussed above, BRG1's association with the promoters of the p16- and p21-encoding genes are enhanced in senescent cells.[6] Upregulation of p16 and p21 by BRG1 depends upon its chromatin remodeling activity.[6] For example, a mutant BRG1 that is defective in its chromatin remodeling activity fails to upregulate p16 and p21 and is also impaired in SAHF formation.[6] This suggests that BRG1 may drive SAHF formation directly via its chromatin remodeling activity and/or indirectly through upregulating p16 and p21 expression.

BRG1 has been shown to interact with pRB,[7] a key regulator of SAHF formation.[1] Interestingly, the interaction between BRG1 and pRB is enhanced during senescence.[6] This correlates with an increased level of BRG1 in the chromatin fraction of senescent cells.[6] A similar increase in BRG1 in the chromatin fraction of senescent cells was also observed using non-biased proteomic analysis of young and senescent cells.[8] Consistent with the idea that the enhanced BRG1 and pRB complex drives SAHF formation, BRG1 overexpression drives SAHF formation, and its knockdown suppresses SAHF formation induced by oncogenic RAS or BRCA1 knockdown.[6] Significantly, BRG1's interaction with pRB is necessary for its ability to drive SAHF formation. For example, a mutant BRG1 that can no longer bind to pRB also fails to induce SAHF formation.[6] Interestingly, the mutant BRG1 remains capable of upregulating p16 and p21.[6] This finding suggests that the interaction between BRG1 and pRB is necessary for

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SAHF formation and likely for silencing proliferation-promoting genes through SAHF formation. However, this interaction is dispensable for upregulating p16 and p21 by BRG1, which depends upon its chromatin remodeling activity.[6]

Oncogene-induced BRCA1 chromatin dissociation contributes to the accumulation of DNA damage in senescent cells due to impaired BRCA1-mediated DNA repair.[2] Interestingly, senescence and SAHF formation induced by ectopic BRG1 is independent of the DDR.[6] These findings suggest that BRG1 and the DDR function independently of each other downstream of BRCA1 chromatin dissociation to promote SAHF formation and senescence.

In summary, BRCA1 chromatin dissociation increases the level of BRG1 in the chromatin fraction of senescent cells. This correlates with an enhanced BRG1 and pRB interaction that drives SAHF formation by silencing proliferation-promoting genes, while upregulating p16 and p21 senescence-promoting factors via BRG1's chromatin remodeling activity in a pRB-independent manner.

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