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Gene regulation and tumor suppression by the bromodomain-containing protein BRD7

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Oncogene-induced senescence (OIS) is a cellular defense mechanism against excessive mitogenic signaling and tumorigenesis. One of the major pathways required for OIS is the p53 tumor suppressor pathway. Consequently, many human tumors harbor *p53* mutations while others show a dysfunctional p53 pathway, frequently by unknown mechanisms. We recently identified *BRD7* as a potential tumor suppressor gene acting as a transcriptional cofactor for p53, affecting histone acetylation, p53 acetylation, and promoter activity on a subset of p53 target genes. We further found low BRD7 expression specifically in a subgroup of human breast tumors harboring wild-type, but not mutant, *p53* and showed that one of the responsible mechanisms is deletion of the *BRD7* gene locus. Here we further discuss the role of BRD7 as a cofactor in transcriptional regulation and highlight its role as a tumor suppressor via association with p53 and other tumor suppressor proteins.

Key words: BRD7, tumor suppressor gene, senescence, p53, transcription, chromatin remodeling

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Introduction

Oncogene-induced senescence (OIS) is an anti-proliferative cellular stress response that serves as an essential intrinsic barrier to tumor development in vivo.[1-3] Although the importance of OIS is acknowledged, the exact mechanism of action is not well understood. Several lines of evidence indicate that oncogene expression, similarly to telomere exhaustion and genotoxic damage, induces the senescence program by activating the DNA damage response (DDR). Specifically, the initial hyper-replication phase fostered by oncogene activity leads to replication stress, which eventually drives cells into senescence.[4,5] Essential for execution of OIS is the p53 tumor suppressor pathway. Activation of this pathway by oncogene expression induces senescence mainly through transcriptional activation of target genes, including the *CDKN1a* gene (encoding the cyclin-dependent kinase inhibitor p21) and *Serpine1* (also known as *PAI-1*, encoding plasminogen activator inhibitor-1[6]). Work with animal models implied that OIS is the major mechanism of tumor suppression by p53 in vivo.[7] Thus, interference with OIS by inhibiting the p53 pathway allows cells to continue to proliferate in the presence of active oncogenes, leading to increased tumorigenicity. Underscoring the therapeutic potential of this pathway, it has been demonstrated that reactivation of p53 in murine tumors causes cellular senescence and associated tumor regression.[8,9] Indeed, DNA-damaging chemotherapeutic agents can induce senescence in cancer cells, which contributes to the anti-tumor effect of these molecules.

Many post-translational modifications have been shown to modulate p53 protein stability, transcriptional activity and selectivity for its target genes. As p53 exerts its multiple functions mainly as a transcription factor, an unresolved issue concerns the routes that lead to specific

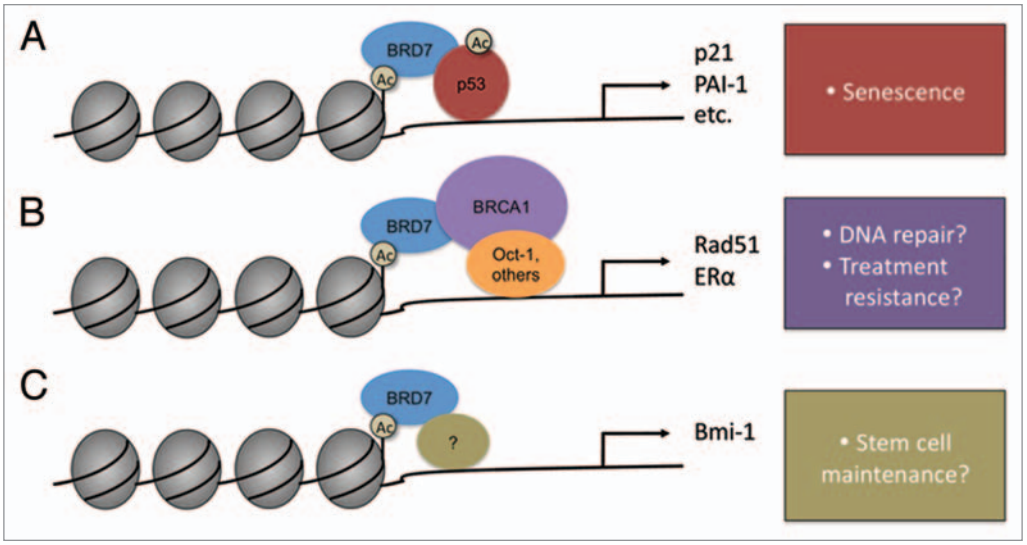

Figure 1. Cell fate determination by BRD7 and mode of action. (A) BRD7 is recruited to p53 target promoters and affects transcription of genes required for oncogene-induced senescence. (B) BRD7-dependent recruitment of Oct1 and BRCA1 to target promoters implies involvement of BRD7 in DNA repair and cancer treatment resistance. (C) A potential role for BRD7 in stem cell self-renewal by regulation of the Bmi1 gene.

cellular outcomes by directing p53's choice between different subsets of target genes. For example, it was shown that acetylation of p53 is necessary for its activation,[10] and acetylation of specific lysine residues on p53 appears to activate different subsets of p53 target genes. Acetylation of lysine 120 within the DNA binding domain of p53 by the acetyltransferase Tip60 was found to specifically direct p53 towards the induction of apoptotic target genes,[11,12] while both acetylation of C-terminal lysine 320 by PCAF, and of lysines 373 and 382 by p300/CBP, have been associated with the induction of p21.[13,14] Therefore, it seems likely that post-translational modifications of the p53 protein determine its functionality in OIS. However, also cell type-specific variations in the availability of certain p53 cofactors, as well as differences in the affinity of p53 and its cofactors for these promoters, have been documented to play a role in determining the eventual fate of a stressed cell.[15]

The central role of the p53 pathway in tumor suppression is reflected in the appearance of *p53* mutations in as many as 50% of human tumors (IARC TP53 Database http://www-p53.iarc.fr/Statistics.html). When the *p53* gene itself is wild-type, genetic lesions in components of the p53 pathway are often found to interfere with its activities. Still, in many cases the mechanism behind the inactivation of this major tumor suppressor pathway is unknown.

BRD7 is a Transcriptional Cofactor Required for p53-dependent OIS

We identified Bromodomain-containing 7 (BRD7) as an important transcriptional cofactor of p53 by combining a loss-of-function screen for putative tumor suppressor genes required for p53-dependent OIS and a two-hybrid screen to fish out novel p53-interacting proteins. Through this approach we concomitantly highlighted the genetic and functional interaction of p53 with BRD7.[16] BRD7 is an evolutionarily conserved protein bearing a single bromodomain.[17] The protein has been shown to be a subunit of SWI/SNF chromatin-remodeling complexes and has been implicated in regulation of transcription.[18,19]

In human primary fibroblasts, knockdown of BRD7 enabled cells to bypass oncogene-induced senescence in the presence of wild-type p53. BRD7 appeared to be required for efficient transcription of a specific subset of p53 target genes that become induced upon expression of Ras^{V12}, including p21, PAI-1, HDM2, Cyclin G1, p53R2, WIG-1, while apoptotic genes were not dependent on BRD7 (**Fig. 1A**). Dissecting the mechanism of functional cooperation of p53 and BRD7, we observed that their interaction is stimulated by Ras^{V12} expression. In these conditions, p53 recruits BRD7 to several of its high-affinity target promoters, including *p21* and *HDM2*. While the BRD7 C-terminus is engaged in binding to p53, its N-terminal domain interacts with the histone acetyltransferase p300. We showed that BRD7 is required for the efficient recruitment of p300 to the *p21* promoter, where it activates transcription by facilitating acetylation of both p53 on lysine 382 and histone H3 on lysine 9 within nearby nucleosomes. Histone acetylation may in turn support the spreading of BRD7 throughout a wider chromatin region, by means of its ability to recognize acetylated histones through the bromodomain.[17,20] Spreading of BRD7 across the chromatin surrounding p53 binding sites is confirmed by the larger amplitude of BRD7 binding peaks as compared to those generated by p53, observed by ChIP-sequencing.[16] It is likely that, through continuous recruitment of p300, this process generates a positive loop that amplifies histone acetylation, thereby sustaining promoter activity.

In addition, BRD7 was recently identified as a component of a SWI/SNF chromatin-remodeling complex.[18] This adds further evidence to the previously described interactions of p53 with other

SWI/SNF subunits, and of the involvement of SWI/SNF activity in p53-dependent transcription.[21,22] SWI/SNF complexes are targeted to promoters via direct interactions with transcription factors.[23] The ability of p53 to independently bind different SWI/SNF subunits suggests that each may have a specific function. Given its role in OIS, it is conceivable that BRD7 may serve for selective recruitment of chromatin-remodeling complexes to p53 target promoters to regulate transcription during OIS. Strikingly, knockdown of the SWI/SNF core ATPase BRG1 has been shown to impair p21 expression[24,25] and this appeared to partially depend on decreased binding of p53 to the *p21* promoter.[26] BRG1 has also been implicated in restraining p53 activity in the absence of DNA damage by cooperating with the E4 ubiquitin ligase CBP.[27] However, our data do not support a role for BRD7 in regulating p53 stability.

Another level of transcriptional regulation by p53 comes from the recent observation that p53 can cause nucleosome repositioning. In unstressed cells, p53 keeps the *p21* promoter in a poised state by directing the binding of the histone variant H2A.Z to p53-cognate sites within the *p21* promoter, thus inhibiting the onset of senescence. Upon DNA damage, p53-dependent activation of the *p21* promoter then involves eviction of H2A.Z.[28] The establishment of the senescent phenotype is accompanied by extensive changes in chromatin structure. In particular, many senescent cells accumulate specialized domains of facultative heterochromatin, called Senescence Associated Heterochromatin Foci (SAHF). SAHF are thought to repress the expression of proliferation-promoting genes, thereby contributing to the senescence-associated proliferation arrest.[29] SAHF formation is a multistep process that involves chromatin-remodeling events and, at least at late stages, requires intact p53 and retinoblastoma (RB) pathways.[30,31] Although SWI/SNF remodeling complexes are involved in RB-dependent repression of E2F target genes[32,33] and induction of cell differentiation and senescence, it is not known whether they may directly participate in SAHF formation. Clearly, it would be of interest to investigate whether BRD7 also acts as a cofactor for RB in the onset of senescence. However, our data do not directly implicate BRD7 in SAHF formation, but rather suggest that during OIS BRD7 is excluded from these structures.[16] This observation is consistent with the report that BRD7 is normally associated with actively transcribed chromatin domains.[19]

Implications for BRD7 in Proliferation, DNA Repair and Stem Cell Biology

As a component of SWI/SNF complexes, BRD7 can be expected to function as a transcriptional cofactor for many other proteins. Moreover, SWI/SNF complexes and BRD7 itself can function both as activators and repressors. This suggests that BRD7 may regulate up to thousands of genes. ChIP-sequencing data highlighted binding of BRD7 to thousands of genomic sites, although we have also observed that BRD7 binding to a promoter does not always imply that the gene is transcriptionally regulated by BRD7.[16] BRD7 targets include proliferation-related genes, such as components of the Ras/MEK/ERK and RB/E2F pathways,[34,35] with consequent inhibition of G_1/S progression.[34]

A role for BRD7 in regulation of genes involved in DNA repair has been highlighted by a recent report showing that BRD7 interacts with the tumor suppressor protein BRCA1.[36] The authors identified a variety of genes co-regulated by BRCA1 and BRD7, including estrogen receptor α, and the DNA repair factor Rad51 (**Fig. 1B**). SWI/SNF complexes have been shown to participate directly in DNA repair, an activity that requires prompt alterations of chromatin accessibility to DDR components. In yeast, SWI/SNF complexes are recruited to DNA double strand breaks (DSBs) to facilitate DNA repair, and mammalian SWI/SNF complexes contribute to DSB repair by stimulating the phosphorylation of histone H2A.X at DSB-surrounding chromatin.[37] Notably, this involves a cooperative activation loop among SWI/SNF, γ-H2AX and H3 acetylation.[38] Furthermore, the catalytic SWI/SNF subunit BRG1 facilitates different stages of nucleotide excision repair (NER). It does so by modulating chromatin relaxation, stimulating stabilization of the xeroderma pigmentosum protein (XPG) at the damaged sites and subsequently stimulating the recruitment of downstream NER factors to UV-induced lesions.[39] Our data do not suggest a role for BRD7 in affecting the persistence of DNA damage signals upon acute genotoxic stress.[16] This points towards a restricted role for BRD7 in the executive, rather than the causative, phases of OIS. However, a potential contribution of BRD7 in the activities of BRCA1 and SWI/SNF complexes in DNA repair remains to be explored.

BRCA1 was previously shown to interact with p53 and regulate its stability and transcriptional activity. Intriguingly, this interaction has been proposed to selectively direct p53 towards induction of genes required for DNA repair and growth arrest,[40] and shifting p53-mediated cellular outcomes towards senescence.[41] The observation that BRG1 is involved in BRCA1-mediated activation of p21 transcription by p53,[42] raises the intriguing possibility that the scaffold protein BRCA1 might contribute to recruit BRD7, and thus SWI/SNF activity, to specific promoters. Based on data of Harte and colleagues, it would be interesting to verify whether BRCA1 is consistently present at promoters co-regulated by p53 and BRD7.[36]

Finally, an intriguing connection of BRD7 with stem cell biology has been proposed while analyzing the consequences of its knockdown on the transcriptional profile of embryonic stem cells.[18] One of the genes induced after BRD7 knockdown was the Bmi-1 oncogene, required for self-renewal properties of stem cells (**Fig. 1C**). This potential function of BRD7 is in agreement with the suggested contribution of senescence to tissue aging, through exhaustion of renewable tissue stem cell populations.[43-45]

BRD7: Another Tumor Suppressor in the SWI/SNF Complex

p53-dependent induction of OIS leads to tumor regression and clearance.[8,9] Our data indicate that impairment of OIS by inhibition of BRD7 allows full neoplastic transformation of both human primary

fibroblasts and mammary epithelial cells in the presence of wild-type p53.[16] Based on this, one could predict that reduced BRD7 expression would be beneficial for pre-tumorigenic cells still containing wild-type p53. Notably, BRD7 is encoded in a locus on chromosome 16q12 that is a well-known hotspot for LOH in breast cancers.[46] Highlighting the relevance of BRD7 for tumor suppression by p53, we found reduced BRD7 expression and deletion of the genomic locus hosting the *BRD7* gene specifically in a subset of breast tumors retaining wild-type *p53*, but not in tumors expressing mutant p53.[16] Loss of BRD7 expression thus provides a means to inactivate the p53 pathway while retaining wild-type *p53*. We are currently analyzing BRD7 expression and localization by immunohistochemistry (IHC) in normal breast tissues and in primary breast carcinomas of which the p53 status is known based on direct sequencing.

Further support for a tumor suppressive role for BRD7 in cancer was found in nasopharyngeal carcinoma (NPC). Low levels of BRD7 were found in these tumors,[47,48] and the majority of NPC tumors have been shown to retain wild-type *p53*.[49] Ectopic overexpression of BRD7 in NPC cells was associated with a proliferation arrest, and with altered expression of genes belonging to Ras/MEK/ERK and RB/E2F pathways.[34] In addition, a CpG island was recently identified in the *BRD7* gene, which is methylated in a large percentage of NPC tumors.[48] We are currently analyzing the methylation status of this CpG island in primary breast tumor datasets, in order to establish whether next to deletion, methylation is also a mechanism to inactivate BRD7 in breast cancers.

Besides allowing pre-tumorigenic cells to grow while expressing activated oncogenes,[16] BRD7 loss may have diverse consequences on the development of breast tumors. Transcriptional profiling and ChIP-sequencing of Ras^{V12}-expressing cells containing BRD7 knockdown suggest that BRD7 regulates genes involved in cell metabolism, DNA repair, as well as putative suppressors of tumor aggressiveness and metastasis.[16] This possibly points to multiple layers of tumor suppression by BRD7. First, BRD7 appeared to be required for the expression of IRS-1 (Insulin receptor substrate 1), a protein that plays a key role in transmitting signals from the insulin and IGF-1 receptors to the PI3K/AKT and Erk/MAP kinase pathways. Suppression of IRS-1 has been reported to promote mammary tumor metastasis in mouse models, and IRS-1 has been frequently found inactivated in human metastatic breast tumors.[50] Second, the involvement of BRD7 in the activities of both p53 and BRCA-1. Somatic loss of BRCA1 and p53 in mice induces mammary tumors with features of human BRCA1-mutated basal-like breast cancer, exhibiting dramatic genomic instability.[51] Third, BRD7 loss could endow breast tumors with resistance to targeted treatments or affect the outcome of chemotherapy. This was recently demonstrated in cells lacking BRD7, where BRCA1-dependent expression of estrogen receptor α is reduced. Consequently, cells were not affected by the treatment with fulvestrant.[36] In addition, cellular senescence contributes to the anti-tumor effect of some genotoxic drugs used for chemotherapy. Our data imply that BRD7 plays a role in p53-dependent transcription in cells treated with etoposide,[16] thereby suggesting that BRD7 may also be involved in p53-dependent senescence in response to drug-induced DNA damage.

Finally, p63 and p73 share many protein partners with p53,[52] and it is then conceivable that BRD7 might also assist specific tumor suppressive functions of p53 family members.[53,54] In particular, it has been reported that TAp63 isoforms are robust mediators of Ras-induced senescence that prevent tumorigenesis in vivo in p53-nullizygous mice,[55] moreover p63 has a crucial role in preventing invasiveness and metastasis of epithelial tumors.[56] It would then be interesting to investigate a possible role of BRD7 in these activities.

In addition to BRD7, several other subunits of chromatin-remodeling complexes have been implicated in human cancer (reviewed in ref. 57). Loss of BRG1, BRM or both was found in 10% to 20% of a range of tumor types, including breast and ovarian tumors.[58-60] SNF5 (Ini1/Baf47/Smarcb1), a core component of the SWI/SNF complex, is a potent tumor suppressor that is consistently lost, mutated or silenced by methylation in pediatric rhabdoid tumors.[61,62]

Concluding Remarks

In this Extra View we discussed the requirement of BRD7 for the tumor suppressive functions of p53, BRCA1, and its role as a component of SWI/SNF chromatin-remodeling complexes. However, many unresolved issues remain. Several of them concern the potential regulation of BRD7 activity by oncogene expression. We have shown that the interaction of BRD7 with p53 increases upon expression of Ras^{V12}. It remains to be determined whether specific oncogene-induced modifications of p53, BRD7 or both are responsible for this. Although we were not able to observe differences in BRD7 expression, stability or subcellular localization in response to Ras^{V12} expression, it is conceivable to assume that post-translational modifications are involved in directing this widespread factor towards specific regulation of senescence-inducing targets. Indeed, we have observed that BRD7 can also bind to p53 target promoters that are not involved in OIS, such as some apoptotic promoters. However, it is not required for their expression upon p53 activation.[16] Can BRD7 then be a determinant for specificity? It has been shown that the presence of specific subunits within the BAF complex affects SWI/SNF target genes differentially, in some cases even antagonistically, determining their gene-specific mode of action.[18] It therefore seems likely that SWI/SNF complexes are involved in the regulation of specific p53 target genes in response to different cellular stresses, thereby determining cellular fate.

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