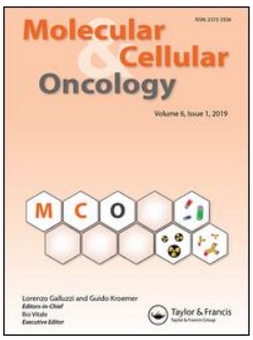

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AUTHOR'S VIEWS

The histone variant macroH2A1 is a splicing-modulated caretaker of genome integrity and tumor growth

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ABSTRACT
The macroH2A1.2 histone variant facilitates the response to replication stress with implications for genome maintenance and cell growth. A mutually exclusive splice variant, macroH2A1.1, has opposing effects on DNA repair outcome and proliferation. Here we discuss the potential impact of splicing-modulated macroH2A1 chromatin organization for cell function and malignant transformation.

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Dynamic changes in chromatin organization are essential for various nuclear processes including transcription, DNA replication and DNA repair. During replication, the encounter of DNA damage or inherently difficult to replicate genomic elements known as fragile sites can result in stalling and/or collapse of the replication fork, eliciting a replication stress (RS) response. The inability of cells to deal with these obstacles interferes with cell division and further poses a risk for genomic integrity, as it can lead to DNA breaks, chromosomal rearrangements and mutations. Consistent with this, fragile sites have been causally implicated in malignant transformation, several chromosome instability (CIN) disorders, and neurodevelopmental diseases. Over the past decade, it has become evident that chromatin plays an essential role in the fine-tuning of the DNA damage response (DDR). While its impact on DNA repair pathways has been studied extensively, how epigenetic changes affect genomic integrity during RS is only emerging.[1]

Recently, we have identified the macroH2A1.2 histone variant as an epigenetic mediator of the RS response.[2] MacroH2A1.2 accumulates preferentially at fragile genomic regions in a manner that depends on DNA damage-induced, *fac*ilitates *t*ranscription (FACT) complex-dependent chromatin remodeling. Together with previous work implicating FACT in the removal of DNA break-associated, serine 139-phosphorylated histone H2AX (γ-H2AX) from nucleosomes,[3] our findings suggest a model in which RS triggers an exchange of γ-H2AX for macroH2A1.2 to bookmark damage-prone genomic regions. Of note, we observed increased macroH2A1.2 accumulation at fragile sites over cumulative cell divisions, pointing to RS as a driver of persistent epigenetic change. Underlining the importance of these findings for genome maintenance, loss of macroH2A1.2 resulted in impaired accumulation of the repair factor BRCA1 at stalled forks and a concomitant increase in RS-associated damage load, which in turn caused increased genome instability in tumor cells and aberrant senescence in primary cells. Altogether, our findings indicate that cumulative RS is necessary to shape a chromatin environment that facilitates an improved RS response in subsequent cell divisions.[2] Intriguingly, an alternative splice variant of the same gene, macroH2A1.1, was shown to have the opposite effect on cell growth and senescence.[4] Furthermore, chromatin immunoprecipitation analyses from our lab revealed no evidence for an RS-induced accumulation of the macroH2A1.1 variant at fragile sites (unpublished). These observations point to distinct, splice variant-specific functions of the macroH2A1.1 and macroH2A1.2 gene products, which are the result of the mutually exclusive incorporation of one of two exon 6 variants within the *H2AFY* gene. Structurally, *H2AFY* alternative splicing results in a 33 amino acid change within the macro-domain that forms a ligand binding pocket for ADP-ribose derivatives specifically in the macroH2A1.1 variant.[5] The latter confers the ability to sense metabolic change as well as respond to pathways that activate poly-(ADP ribose) polymerase (PARP) enzymes. As a result, macroH2A1.1 has been implicated in PARP-dependent DNA repair as well as telomere maintenance and was found to be recruited to sites of DNA damage via its poly-(ADP-ribose) (PAR) binding domain.[6,7] Interestingly, macroH2A1.2, which lacks the ability to bind PAR, has also been implicated in DNA repair, but shows distinct recruitment and repair characteristics.[8] Most notably, while macroH2A1.1 has been associated with repair via non-homologous end joining,[7] we found that macroH2A1.2 has little effect on this pathway but instead promotes homologous recombination through its ability to retain BRCA1 at DNA breaks and sites of RS.[2,8] Together with their opposing impact on cell growth, these results raise the intriguing possibility that macroH2A1 splice variants represent distinct modes of chromatin function, thus extending the existing histone variant code.

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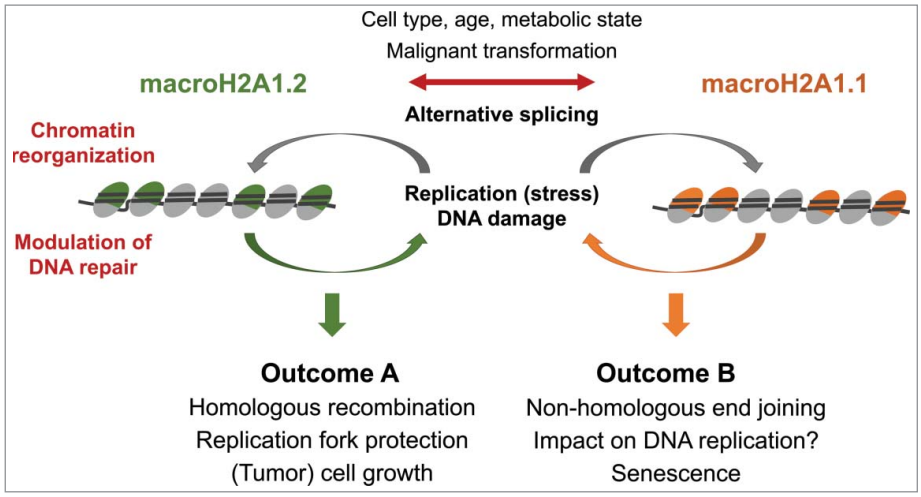

Figure 1. *H2AFY* alternative splicing as a modulator of chromatin-directed genome maintenance. DNA damage or replication stress result in chromatin reorganization involving macroH2A1 histone variants. Alternative splicing of the *H2AFY* gene may shift the chromatin landscape towards one or the other macroH2A1 splice variant with distinct outcomes for DNA repair and cell function.

Consistent with the notion that alternative splicing is often influenced by cell type, age, and malignant transformation, the expression of macroH2A1 variants is developmentally regulated, exhibits a tissue-specific preference, and shows a strong bias in cancer.[6] In agreement with its role during replication stress, macroH2A1.2 expression is particularly prominent in dividing, less differentiated cell types, including embryonic stem cells, whereas macroH2A1.1 expression increases upon cellular differentiation.[6] Similarly, macroH2A1.2 is the predominant and sometimes sole, detectable isoform in a variety of cancers.[9] To date, there are only three known modulators of macroH2A1 alternative splicing, the RNA helicases DDX5 and DDX17 and the spicing factor QKI, which inversely correlates with macroH2A1.2 expression in tumor cells.[9,10] To fully understand the mechanistic basis for *H2AFY* alternative splicing, a comprehensive dissection of developmentally regulated and/or cancer-associated splicing factors will be essential. Underlining the physiological consequences of macroH2A1 variant bias during malignancy, overexpression of macroH2A1.1 but not macroH2A1.2 suppresses tumor growth, at least in part by promoting a senescence-associated secretory phenotype and concomitant irreversible cell cycle arrest.[4] Conversely, macroH2A1.2 facilitates tumor growth by protecting from excessive RS-induced DNA damage.[2] Taken together, these findings suggest that targeting *H2AFY* alternative splicing may serve as a novel therapeutic strategy to prevent or interfere with tumorigenesis.

In summary, we propose that the two splice variants of *H2AFY*, macroH2A1.1 and macroH2A1.2, establish functionally distinct chromatin environments that differentially affect at least two central aspects of cell function, genome maintenance and the control of cell growth (Fig. 1). While the ability to bind PAR is no doubt an important aspect of macroH2A1.1 function, it fails to explain the unique roles of the macroH2A1.2 variant. Analyses of macroH2A1 splice variant interactomes as well as their potentially distinct chromatin landscapes are, therefore, needed to better understand how a modest difference in the macro-domain structure can have such pronounced, opposing physiological consequences.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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