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Antisense protein of HTLV-2 (APH-2) associates with PML nuclear bodies: molecular determinants and functional implications

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Antisense Protein of HTLV-2 (APH-2) was described in 2009. APH-2 mRNA is expressed *in vivo* in most HTLV-2 carriers. In recent years, several laboratories have searched for similarities and/or differences between APH-2 and the antisense protein of HTLV-1, HBZ. Similarly to HBZ, APH-2 negatively regulates HTLV-2 transcription. However, it does not promote cell proliferation. *In vivo*, APH-2 localizes in discrete nuclear domains distinct from nucleoli. We therefore characterized APH-2 subcellular localization, in order to decipher the determinants of such localization and to correlate it or not with APH-2 functions. We first identify APH-2-containing nuclear domains as PML nuclear bodies (PML-NB). PML-NB are modulators of a number of cellular processes ranging from transcription regulation to cell proliferation and death. We show that both an *in silico*-identified nuclear localization signal and the carboxy-terminal LXXLL motif contribute to APH-2 targeting to PML-NB. Covalent modification of APH-2 by SUMO-1 and non-covalent interaction between APH-2 and SUMO-1-modified cellular partners have also been investigated as mechanisms of APH-2 targeting to PML-NB. Our results further demonstrate that APH-2 association with PML-NB is critical for its ability to inhibit viral transcription. This association also leads to a striking decrease in APH-2 stability, suggesting that APH-2 might be active but also targeted to degradation in PML-NB. Finally, we show that APH-2 localization in PML-NB leads to PML-NB clustering and correlates with a decrease in cell proliferation. Altogether, our study sheds new light on the links between the subcellular localization of APH-2 and its cellular functions.

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