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Poster presentation

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Antagonistic effect of the tumor suppressor Menin and the HBZ protein of HTLV-I on telomerase activity

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Background

HTLV-1 is a retrovirus responsible for adult T-cell leukemia (ATL) in 5% of infected people. ATL is characterised by a monoclonal proliferation of infected CD4+ T lymphocytes in which a high telomerase activity associated to a poor prognosis has been observed [1]. Furthermore, HBZ is the only viral protein clearly detectable in all ATL patient samples. This protein has been shown to up-regulate the transcription of the catalytic subunit of telomerase, hTERT. Therefore interaction of HBZ with AP-1 transcription factor JunD on the proximal promoter of hTERT is required to up-regulate the gene [2].

Menin, a tumor suppressor, is known as a repressor of both JunD transcriptional activity [3] and hTERT transcription [4]. These data led us to investigate the mechanisms underlying hTERT up-regulation by HBZ and JunD in the presence of Menin.

Results

Thus we have shown that HBZ is able to counteract the inhibitory effect exerted by Menin on JunD transcriptional activity in a dose dependent manner. HBZ is also able to partially restore endogenous telomerase activity in spite of the Menin presence. HBZ and JunD have been shown to co-immunoprecipitate with Menin protein suggesting that HBZ does not counteract Menin by evicting it from the complex. Menin repress JunD transcriptional activity through the recruitment of histone deacetylases

whereas HBZ interacts with p300, an histone acetyl transferase. Thus we have demonstrated that p300 recruitment by HBZ is necessary to stimulate JunD transcriptional activity and hTERT proximal promoter in the presence of Menin.

Similarly to hTERT and JunD which are highly expressed in ATL cells, Menin mRNA are clearly detectable in primary ATL cells underlying the importance for HBZ to be able to counteract the repression exerted by this tumor suppressor.

Conclusion

Our findings provide further insights in the mechanism of hTERT up-regulation by JunD and HBZ and ascertain Menin as a new player in the ATL leukemogenic process.

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