UNIVERSITÀ DEGLI STUDI DI UDINE
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CORSO DI DOTTORATO DI RICERCA IN:
SCIENZE BIOMEDICHE E BIOTECNOLOGIE

HDAC4/HDAC3 COMPLEXES ANTAGONIZE p300/AP-1 ACTIVITIES ON WELL-DEFINED SUPER-ENHANCERS

keywords: HDAC4, senescence, SEs, SASP, HDAC3, p300, AP-1

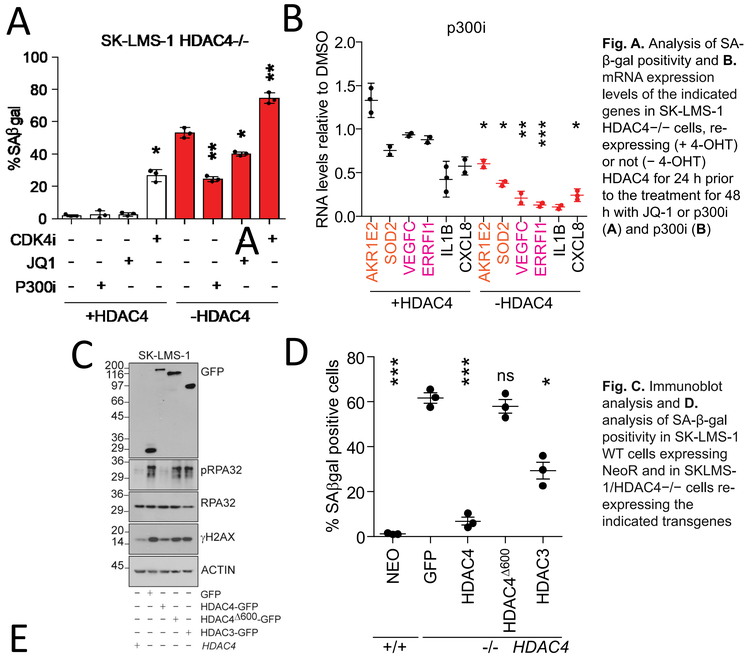

Fig. A. Analysis of SA-β-gal positivity and **B.** mRNA expression levels of the indicated genes in SK-LMS-1 HDAC4−/− cells, re-expressing (+ 4-OHT) or not (− 4-OHT) HDAC4 for 24 h prior to the treatment for 48 h with JQ-1 or p300i (**A**) and p300i (**B**)

Fig. C. Immunoblot analysis and **D.** analysis of SA-β-gal positivity in SK-LMS-1 WT cells expressing NeoR and in SKLMS-1/HDAC4−/− cells re-expressing the indicated transgenes

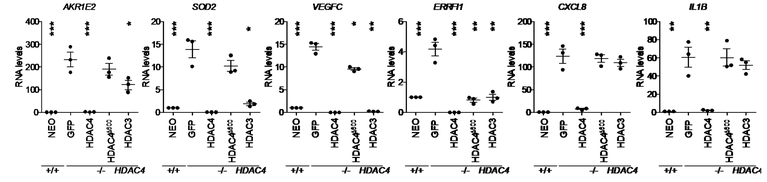

Fig. E. mRNA expression levels of the indicated genes in SK-LMS-1 WT cells expressing NeoR and in SK-LMS-1/HDAC4−/− cells re-expressing the indicated transgenes

AIMS:

Taken together, the results presented in this thesis highly contribute to enhancing our understanding of the epigenetic role of HDAC4 in regulating the chromatin state of senescent cells. In particular, the project highlights the key role of HDAC4 as an epigenetic reader involved in the regulation of senescence-associated enhancer (TEs) and super-enhancers (SEs) that supervise the senescence program. Moreover, with our work we aim to identify the HDAC4-associated partners that are recruit as high molecular weight complexes at TEs and SEs chromatin distal regulative elements.

APPLICATIONS:

An exciting new prospect arising from these findings could be the identification of novel therapeutic approaches based on specific inhibitor for HDAC4 to induce a senescence response and enhance a proinflammatory state (SASP response) to target different age-related diseases including cancer.

RESULTS:

The epigenome of senescent cells undergoes a deep redistribution of H3K27 acetylation. The class IIa Histone Deacetylases (HDAC4,5,7,9) are recruited on chromatin for the rapid de novo deacetylation of H3K27ac loci as part of large repressive complexes through their binding of class I HDACs. We found that HDAC4 is post-transcriptionally downregulated during aging and senescence. Moreover, HDAC4 knock-out (KO) triggers premature senescence in cancer cells through the activation of TEs and SEs supervising the senescence program and particularly the SASP response. We also found that the depletion of HDAC4 promotes the expression of endogenous retroviruses (ERVs) leading to the activation of SASP response through the engagement of a specific family of cytosolic immunosensors. The data regarding the relationship between HDAC4 and ERVs during the senescence response and the role of ERVs deregulation in the accomplishment of senescence program are now under revision for publication.

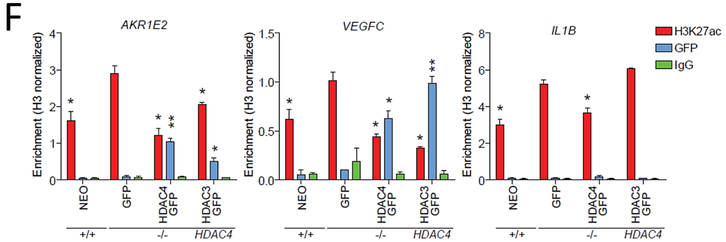

Fig. **F**. ChIP-qPCR signals, normalized to total H3, obtained for the indicated antibodies in the indicated cells.