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NOV 9, 2021 – 1:30 PM
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UNVEILING THE THERAPEUTIC POTENTIAL OF HDAC8 INHIBITION BY USING BOTH IN VITRO AND IN VIVO (DANIO RERIO) MODELS

Marco Spreafico

Dipartimento Biometra, Università degli Studi di Milano

The use of pan-histone deacetylase inhibitors (HDACi) for disease treatment has gained an interest in recent years, albeit exhibiting low specificity, variable efficacy and side effects. Therefore, the identification of the potential of individual HDAC as pharmacological target may improve therapy outcome, circumventing the adverse effects of pan-HDACi. Histone deacetylase 8 (HDAC8) is a class I HDAC that possesses a unique structure that allows the development of highly specific inhibitors, such as PCI-34051. By using both cell lines and zebrafish (Danio rerio), we have assessed the feasibility of PCI administration as a pharmacological approach in the treatment of two pathologies characterized by HDAC8 overexpression: acute myeloid leukaemia (AML) and Duchenne muscular dystrophy (DMD). Concerning AML, we observed cell cycle arrest and apoptosis induction following PCI treatment in both AML cell lines and in the haematopoietic stem cell population of hdac8-overexpressed zebrafish embryos. Our analysis identified both p53-dependent apoptosis and canonical WNT pathway modulation as mechanisms underlying the anti-leukemic effect of HDAC8 inhibition by PCI. Concerning the DMD phenotype, PCI treatment ameliorated the fusion index of DMD myotubes and increased myosin expression in dystrophic zebrafish embryos. To discover HDAC8 targets, we performed acetylome profiling in zebrafish embryos treated or not with PCI and identified several cytoskeleton proteins differently acetylated. Among them, a-tubulin acetylation was increased in dystrophic zebrafish and was restored by PCI treatment, together with the rescue of cytoskeleton architecture alterations which are a typical feature of DMD condition. Our results suggest that selective inhibition of HDAC8 by PCI-34051 possesses a promising potential as a therapeutic approach for both AML and DMD treatment.

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