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TARGETING MYC OVEREXPRESSING LEUKEMIA WITH CARDIAC GLYCOSIDE PROSCILLARIDIN THROUGH DOWNREGULATION OF HISTONE ACETYLTRANSFERASES

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Targeting MYC remains a major therapeutic goal in cancer chemotherapy. Here, we identified that proscillaridin, a cardiac glycoside approved for heart failure treatment, targets specifically leukemic cells overexpressing MYC at clinically relevant doses. Proscillaridin induced rapid downregulation of MYC proteins, reduced proliferation in leukemic cell lines and in leukemic stem cell populations. Transcriptomic profile of leukemic cells after treatment showed a downregulation of gene sets involved in cell replication, MYC pathways and an upregulation of genes involved in hematopoietic differentiation. Interestingly, low dose of proscillaridin treatment induced a significant loss of lysine acetylation on histone H3 at lysine 9, 14, 18 and 27. Acetylome profiling uncovered that acetylation loss included also non-histone proteins such as MYC itself, MYC target proteins, and a series of histone acetylation regulators. Loss of acetylation resulted from the rapid downregulation of histone acetyltransferase proteins after treatment. Overall, these results strongly support the re-purposing of proscillaridin in MYC overexpressing leukemia and suggest a novel strategy to target indirectly MYC by inducing the downregulation of a series of histone acetyltransferases involved in its stability.

Biography

Noël J-M Raynal has completed his PhD from University of Québec and Postdoctoral studies from MD Anderson Cancer Center and Temple University. He is the Director of an academic laboratory at the Centre de recherche of CHU-Sainte-Justine in Montreal affiliated with the Department of pharmacology and physiology of the Université de Montréal. His research focuses on epigenetic therapy of pediatric cancers.

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