Category: Basic Research

Possible role of Chaetocin in reversing of Prelamin A accumulation and HIV latency in HIV infected individuals

Pragati Chavan, Anuja Sonawane, Jyoti Sawant, Pallavi Shidhaye, Amrita Rao, Rajani Bagul, Ujjwala Ghule, Sunita Kumbhar, Manisha Ghate, Ashwini Shete

Affiliation: ICMR-National Institute of Translational Virology and AIDS Research (formerly ICMR-National AIDS Research Institute), Pune

Background:
Prelamin A, a precursor of lamin A, gets accumulated in response to oxidative stress and has been implicated in premature and physiological aging. Accumulated Prelamin A induces DNA damage causing genomic instability and premature senescence. Since HIV infection is characterized by chronic oxidative stress, we assessed if HIV infected cases have higher Prelamin A levels as compared to HIV uninfected controls. We also investigated effect of histone methyltransferase inhibitor on Prelamin A and P24 expression in the cases as depleting Suv39h1 results in improved DNA repair mechanisms and HIV latency reversal.

Methods:
The study was conducted in asymptomatic virally suppressed HIV infected patients on ART for more than 5 years [n=70, M:F=36:34] and HIV uninfected controls [n=68, M:F=31:37] in the age-group of 40-55 years. Blood samples were collected for assessing levels of Prelamin A accumulation in CD4 and CD8 T cells by flow cytometry. PBMCs of the study participants were treated with Chaetocin (400nM), a histone methyltransferase inhibitor, to assess its effect on Prelamin A accumulation and intracellular P24 expression in HIV infected individuals. Prelamin A levels were analysed for their correlation with immunosenescent markers.

Results:
Higher median fluorescence intensity of Prelamin A expression was observed in CD4 and CD8+T cells ($p<0.0001$) in HIV cases as compared to control samples. Prelamin A accumulation in CD4+T cells correlated significantly with the frequency of CD57+CD4+T cells ($r=0.237, p=0.038$) as well as CMV IgG index ($r=0.229, p=0.049$). Prelamin A accumulation in CD4+T cells diminished significantly after treating them with Chaetocin (0.0273). P24 expressing CD4+T cells increased significantly after Chaetocin treatment ($p=0.0294$).

Conclusion: Prelamin A accumulation, a marker of DNA damage, might be used for detecting premature aging in HIV individuals. Possible role of histone methylation modulators in reversing premature aging as well as HIV latency needs to be explored further.