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HIV-1-MEDIATED INSERTIONAL ACTIVATION OF STAT5B AND BACH2 TRIGGER VIRAL RESERVOIR IN T REGULATORY CELLS

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It has been shown that HIV-1 insertions targeting BACH2 and STAT5B are enriched and persist for decades in hematopoietic cells from patients under Anti-Retroviral Therapy (ART), suggesting that insertional mutagenesis could provide a selective advantage to these cell clones. However, the mechanisms used and the physiological impact on the cells harboring these integrations are completely unknown.

In the hematopoietic cells of 30/87 patients under ART we identified chimeric mRNA containing viral HIV-1 sequences fused to the first protein-coding exon of STAT5B or BACH2. By performing droplet digital PCR, we found that these chimeric mRNAs were specifically enriched ($p<0.001$) in T regulatory (Treg) cells in all patients tested (N=9). Forced expression of *STAT5B* and *BACH2* in Treg cells purified from healthy donors did not alter their phenotype and functions *in vitro* and significantly increased their proliferative capacity in competitive proliferation assays ($p<0.0001$). Co-injection in immune-deficient mice of GFP-, BACH2- and STAT5B-transduced Treg cells with allogenic PBMCs prevented xenogeneic graft-versus-host disease in 75% of the animals and reduced the level of human chimerisms in the blood of mice receiving STAT5B-expressing Treg cells when compared to mice treated with GFP-expressing Treg cells ($p<0.001$), suggesting for a superior activity of STAT5B-expressing cells in controlling the expansion of human PBMC.

These data provide evidences that HIV-1 takes advantage of insertional mutagenesis to favor its persistence in the host by infecting long-living and self-renewing cellular reservoir endowed with the ability to diminish the immune surveillance against infected cells.

New targeted therapies aimed at interfering with BACH2 and STAT5B pathways could be exploited to reduce cellular reservoirs and favor the eradication of the infection in cART-treated patients.

Biography

Eugenio Montini obtained his Ph.D in the field of human molecular and medical genetics at the Telethon Institute of Genetics and Medicine (TIGEM, Milan, Italy) and later at the Oregon Health Science University (Portland, USA) as American Liver Foundation Amgen and HIH Postdoctoral Research Fellowship Awardee in the field of viral and non-viral mediated gene therapy. He is now Group Leader of the Vector Safety and Insertional mutagenesis Reseach Unit and Vector Integration Core and is a word leading expert in insertional mutagenesis and genotoxicity by HIV-1 and derived vectors (Montini et al., 2006 Nature Biotechnology; Ranzani et al., 2013 Nature Methods; Biffi, Montini et al., 2103 Science, Aiuti et al., 2013 Science; Cesana et al., 2017 Nature Communications).

He authored 60 publications in peer reviewed journals with 4611 citations and an H index of 31.

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