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Commentary

Flower power: Locking HIV in the gut with French lilac

Olivier Rohr

Université de Strasbourg, UR 7292, FMTS, IUT Louis Pasteur, Strasbourg, France

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Despite major advances in the treatments of people living with HIV (PLWH), patients are still subjected to life-long antiretroviral therapies (ART). More importantly, during ART, residual HIV-1 gene transcription occurs at very low levels in cellular and anatomic reservoirs. This residual transcription is associated with chronic immune activation and low-level inflammation states that promote non-AIDS co-morbidities [1]. Delphine Planas and colleges [2] report that 12 weeks oral administrations of metformin reduced HIV-1 gene residual transcription in the gut-homing CD4+CCR6+ T cells reservoirs and limit their infiltration in the colon. Mechanistically, the results suggest that metformin treatment selectively reduced mTOR activation in reservoir cells from sigmoid colon biopsies to repress residual viral transcription. Since the reservoirs and the inflammation markers in the blood were not impacted, the results suggest that metformin promotes a mTOR-driven, gut specific lock of HIV-1 gene expression associated with a reduced local inflammation.

Derived from French lilac compounds in 1920s, metformin has been widely used to treat type 2 diabetes. Metformin acts as a diet mimetic agent and promotes weight loss in diabetic and non-diabetic subjects. The growth differentiation factor 15 (GDF-15) mediates these beneficial effects. Metformin stimulates GDF-15 secretion in the gut to control the gut-brain axis dedicated to the regulation of food intake [3]. Composition of the gut microbiota has been associated with disease outcome in ART-treated PLWH. 12-weeks of metformin treatments increased the abundance of anti-inflammatory bacteria in the gut of non-diabetic PLWH [4]. All these results suggest that Metformin preferentially impacts the gut, one of the anatomic HIV-1 reservoirs.

Several anatomic reservoirs have been identified including the blood, the lymph nodes, the male genital track, the brain and the gut associated lymphoid tissues (GALT). In these anatomic compartments, cellular reservoirs hide latently integrated HIV-1 provirus in their own genome. These infected cellular reservoirs constitute major hurdles toward a HIV cure. They can expand and contract despite ART. Expansion of the reservoir cells contributes to the persistence of the virus. A recent study from Nicolas Chomot's lab reports that "CD4 + T cells reservoirs are the progeny of infected central memory cells undergoing antigen-driven clonal expansion during ART" [5]. These results further highlight that ART is needed to control active viral replication but inefficient to control the dynamic of the reservoir and to overcome chronic immune activation.

A number of studies have reported that efficiencies of HIV cure interventions on viral reservoirs depend on the reservoir type (for review [6]). Reactivation of the latent HIV (shock) to reduce the cellular reservoirs by a boosted immune system (kill) is one of the strategies tested to promote a functional cure. Despite some shock and kill strategies producing unconvincing results, more recent publications demonstrated the relevance and the efficiency of the shock to reactivate latent HIV and SIV from the blood and the tissue reservoirs in vivo [7]. As stated above, reservoirs are heterogeneous in their type, localization and in the molecular mechanisms controlling viral latency. To overcome the heterogeneity of HIV-1 cellular and tissue reservoirs, shock strategies will need patient-adapted combinations of LRA delivered in appropriate timings [8,9]. Another strategy aims to "block and lock" the HIV into deep latency to promote a functional cure [10]. Didehydro-Cortistatin A (dCA) that targets HIV-1 Tat protein, is one of the more promising molecules for the block and lock strategy [11]. However, whether dCA treatments reduce the residual inflammation and the constitutive activation of the immune system remains unclear. Defining the best molecular targets is a prerequisite to an efficient HIV cure strategy. One such target is the mTOR cellular complex that has been described to control different steps of the HIV-1 life cycle including viral gene transcription and latency ex vivo [12,13]. However, no reactivation of the latent HIV was observed in vivo due to the poor pharmacodynamic properties of the mTOR activator tested [13]. Interestingly, Jean-Pierre Routy's group previously reported that mTOR is a key contributor to HIV-1 permissiveness in gut-homing th17-polarized CCR6+CD4+ T cells, giving new opportunities for specific therapeutic approaches in vivo [14]. In addition, metformin has been described to influence many physiological functions and pathways including mTOR [15]. In the present article, the authors describe a pilot trial aiming to define the influence of metformin treatment on the HIV-1 reservoirs in the blood and the colon. Since metformin had no influence on the blood reservoirs but significantly reduced residual HIV-1 gene transcription in the gut-reservoir, this proof-of-concept study suggest that metformin may be a good candidate for block and lock strategies. Future clinical trials including more PLWH will be needed to confirm the hope put on metformin.

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E-mail address: olivier.rohr@unistra.fr

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However, as shown for the mTOR / metformin story, one should keep in mind that efficient HIV cure strategies will emerge from molecular virology investigations to find the best therapeutic targets, ex vivo experiments to test the best combinations of molecules, in vivo experiments to ensure a good pharmacodynamic of the molecules of interest and finally clinical trials. Basic science gives hope that guides clinical science toward the treatments and the cure of patients.

Contributions

OR conceived and wrote the article

Declaration of Competing Interest

OR declares no conflict of interest

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