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miRs – Novel Tools to Block Gut Inflammation in HIV?

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While modern antiretroviral therapy (ART) has dramatically improved the health and life expectancy of HIV-infected individuals, they remain at much higher risk for morbidity and mortality than the general population. One of the key drivers of this risk is thought to be the persistence of immune activation and inflammation despite ART-mediated viral suppression. While many factors likely contribute to this persistent inflammatory state, gut epithelial barrier dysfunction and microbial translocation is likely to play a major role [1]. Indeed, microbial translocation is induced in the first few days of pathogenic SIV infection, even before viremia is apparent [2]. Gut barrier defects are also detected during the very earliest stages of HIV infection [3]. While soluble markers of gut epithelial barrier integrity improve during antiretroviral therapy, they remain persistently abnormal even with sustained viral suppression, particularly when ART is delayed until advanced disease stages, and these markers strongly predict increased mortality in this setting. It is widely believed that persistent inflammation in the gut mucosa is at least partly responsible for these gut barrier defects as appears to be the case in murine models of inflammatory bowel disease. Thus, restoring gut epithelial barrier function – perhaps by first decreasing mucosal inflammation – has emerged as a major HIV research priority. Yet, initial attempts at reversing gut barrier defects and microbial translocation in both untreated and treated HIV infection have been unsuccessful to date [4, 5].

In their manuscript in this issue of *AIDS*, Fulcher et al identify a potentially novel target for interventions to reduce mucosal inflammation in HIV infection, and by extension, microbial translocation [6]. MicroRNAs (miRs) are a recently described subset of nucleic acids that perform a variety of signaling activities both within and between cells and several have been shown to exert immunologic effects. Fulcher *et al* identified a number of miRs that appeared to be significantly up- or downregulated in untreated HIV infection and then focused their attention on two miRs, miR-26a and miR-29a, that were both significantly downregulated in colonic tissue from viremic participants and were known to be associated with blunting of IL-6 signaling pathways – one of the key inflammatory cytokines that predicts mortality and that is upregulated in the gut mucosa in treated HIV infection [7]. Interestingly, in tissues from HIV-uninfected participants with inflammatory bowel disease, these same miRs were increased, not decreased; presumably as a regulatory response to inflammation [8]. They

replicated their “hits” in an independent sample of HIV-infected individuals, demonstrated that these miRs were also reduced in CD4+ T cell lines infected with HIV (within hours, before there would be expected to be much cell death) and also human colonic tissue explants infected with HIV. They then confirmed that these miRs bind to the 3’UTR in IL-6 and STAT3 genes and directly suppressed IL-6 transcription when overexpressed in Jurkat cell lines. Taken together, these data demonstrate a previously unidentified role for miRs in modulating inflammation in the context of HIV infection.

This impressive amount of work revealed a potentially novel mechanism by which HIV may increase IL-6 expression (and its signaling pathways), which has been strongly predictive of clinical outcomes in treated HIV infection [7, 9, 10]. While the degree to which these miRs are major determinants of IL-6 expression *in vivo* (as opposed to other pathways that induce IL-6) as well as the specific mechanisms by which HIV suppresses miR expression remain unclear, this work identifies a potentially novel mechanistic pathway to reduce IL-6 levels in treated HIV infection. A potentially even greater unresolved question is whether an intervention that reduces mucosal IL-6 levels might have unintended negative consequences on gut barrier function in treated HIV infection. For example, the incomplete recovery of Th17 and other IL-17 and IL-22-expressing cells in the gut mucosa is thought to be one mechanism to explain persistent microbial translocation in treated HIV infection given the important role these cytokines play in supporting tight junctions between epithelial cells, antimicrobial peptide secretion, and attraction of neutrophils to clear translocated microbial products [11]. Since IL-6 is a key cytokine supporting the differentiation of Th17 cells [12], it is possible that suppressing IL-6 in the gut mucosa might have the unintended consequence of further reducing Th17 cells, potentially compromising gut integrity despite a reduction in mucosal inflammation. This hypothesis could be addressed in future interventional studies.

These data may also have broader implications for inflammatory diseases other than HIV, where IL-6 signaling is thought to play an important role. Nevertheless, the root drivers of the inflammatory state and the mechanistic pathways driving downstream IL-6 associated inflammation may vary between different inflammatory disease states. For example, inflammatory bowel disease is characterized by an abnormal increase in Th17 cells in the gut mucosa, which is thought to play an active role in promoting inflammation in that setting, the exact opposite of what is observed in HIV-infected individuals [13]. Thus, miR-mediated reductions in IL-6 might plausibly have an even greater benefit in the context of inflammatory bowel disease than in HIV as the expected reduction in Th17 cells with reduced IL-6 signaling might actually be beneficial in that setting. Thus, the relative balance of positive and negative immunologic effects of miR-mediated IL-6 reduction may depend on the underlying disease state. These considerations strongly support the view that the effects of immune-based interventions in other inflammatory diseases or the general population cannot necessarily be generalized to treated HIV infection. Such interventions need to be studied in the context of treated HIV infection, where the balance of positive and unintended negative immunologic effects may be different.

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