

Potential of Prebiotics and Probiotics to Enhance the Efficacy of HIV Vaccination: A Working Hypothesis

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Globally, acquired immunodeficiency syndrome (AIDS) is an epidemic, severe and fatal disease. Extensive research to develop a vaccine for AIDS has been undertaken. Question is whether or not prebiotics and probiotics are effective in human immunodeficiency virus (HIV) vaccination? The answer might partially lay in heat shock proteins (HSPs).

HSPs, a class of functionally related proteins whose expression is increased when cells are exposed to elevated temperatures or other stress [1] of different origins, with molecular weights of about 60, 70, and 90 kDa, play a pivotal role in viral infections, including HIV [2]. HSP70 plays an important role in the life cycle of HIV-1 virus [3] and is over expressed in HIV-infected cells, and this is the most abundant HSP associated with HIV virions [4]. HIV-infection induces a marked increase in the anti-HSP70 antibody levels [4,5], which is consistent with the enhanced expression of HSP70 on the surface of HIV-infected cells and/or incorporation of the protein into the membrane of HIV virions; highly active antiretroviral therapy leads to normalization of the levels of anti-HSP70 [5]. It is promising that prebiotics/and or probiotics can enhance some HSPs, such as HSP70, which are important in HIV patients. Probiotics/and or prebiotics have been examined for their effectiveness in the prevention and treatment of a diverse spectrum of disorders, however, there is currently no clinical trial investigating their effectiveness in HIV vaccination. More knowledge about the interplay between the innate and adaptive immune responses, and nutrient-induced modulation in HSP levels is important to develop new HIV vaccine strategies. It has been shown that nutrients and dietary interventions can modulate HSP levels in animals [6-17] and in humans [18]. In this paper, we overview some evidence regarding potential beneficial effects of such prebiotic and/or probiotic dietary supplementation in connection with HIV vaccines. Implications of this hypothesis cover other similar situations.

HSP binding to viral complexes can enhance antiviral immunity, including natural killer, antibody-dependent, gamma delta T-cell and cytotoxic T-lymphocyte activities against HIV-1 infected cells [19,20]. On the other hand, there are reports of enhanced HSP70 expression following a dairy strain of *Lactobacillus helveticus* MIMLh5 supplementation in FaDu cells in the human pharynx [21], *Escherichia coli* Nissle in gastric cells in rats [22], in enterocyte-like Caco-2 cells after exposure to non-starter lactobacilli [23], enhanced HSP27 followed by *Bacillus subtilis* supplementation in humans [24]. Furthermore, prebiotics have been shown to overexpress HSP25 in colonic mucosa in rats [25].

Another novel and important finding from a recent study was that the levels of some key regulatory proteins were elevated in Caco-2 cells in response to contact with *Lactobacillus fermentum* I5007. They include spectrin-a, major vault protein, voltage-dependent anion channel-1, glutathione transferase, and HSP gp96. HSP gp96 (an endoplasmic reticulum protein) and they are different from other HSP proteins and they play an important role in the immune

response [26]. It should be reminded that strong CD4+ and CD8+ T cell responses are considered important immune components for controlling HIV infection and their priming may be central to an effective HIV vaccine. Goulder and colleagues described an approach by which multiple CD4+ and CD8+ T cell epitopes are processed and presented from an exogenously added HIV-1 Gag-p24 peptide of 32 aa complexed to HSP gp96. CD8+ T cell recognition of the HSP/peptide complex, but not the peptide alone, was inhibited by brefeldin A, suggesting an endoplasmic reticulum-dependent pathway. Their study is the first report to describe an efficient processing and simultaneous presentation of overlapping class I- and class II-restricted epitopes from the same extracellularly added precursor peptide complexed to HSP. Their data suggested that HSP-complexed peptides containing multiple MHC class I- and class II-restricted epitopes represent potential vaccine candidates for HIV and other viral infections suitable to induce effective CTL memory by simultaneously providing CD4 T cell help [3].

Currently, one HSP, the endoplasmic reticulum stress-response protein Gp96 is undergoing clinical trials for cancer treatment and has yielded promising results, including the induction of anti-tumor immunity and some benefit for patients when administered as part of a multidose regimen.

We hypothesize that artificial over-expression of HSPs might enhance efficacy of HIV vaccination in humans. There is only one case report of a patient who developed bacteraemia and septic pulmonary emboli with *Lactobacillus acidophilus* after taking a probiotic containing this organism [27], however, *S.boulardii* has been used to treat 33 HIV patients with chronic diarrhea. In these double-blind studies, 56% of patients receiving *S.boulardii* had resolution of diarrhea compared with only 9% of patients receiving placebo. There were no case of bacteraemia and septic pulmonary emboli in either study [28,29]. Overall, such studies will also give encouragement to industries to think about possibility of pre/probiotic formulations for a higher efficacy of HIV vaccination, worldwide.

At present, there are not sufficient published works to perform a comprehensive review. Nevertheless we encourage researchers to

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consider this interesting topic, while making subsections to HSPs, pre/pro biotics and viral infections. We hypothesize that different pre / probiotics might influence different HSPs in a different manner and therefore viral infections patho-mechanisms, consequently.

Also, it will be helpful to address the questions whether pre/pro biotics elevate HSPs by involving HSF-1, whether such an increase is a result of stress, and how do elevated intracellular levels of HSPs contribute to T cell responses? Keep in mind, in most adaptive immune responses the HSPs have been administered exogenously. And finally, but not least important, are elevated levels of HSP good or bad for viral infection since it seems all might be true.

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