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Commentary

Antiviral activity of cystatin C against HIV

There is no effective vaccine against HIV till date. Treatment with highly active antiretroviral therapy (HAART) helps in reducing viral load and delaying disease progression, although it is not possible to completely eliminate HIV with ART[1]. An overall marked reduction in adult HIV prevalence and new infections has been observed in India[2]. The wider access to ART has resulted in a decline of the number of people dying due to AIDS related causes. The antiretroviral therapy targets at restricting HIV replication, restoring and preserving the immune system, improving survival and the quality of life, reducing HIV related mortality and morbidity in addition to reducing HIV transmission and preventing new infections[3]. However, HIV-infected individuals on ART continue to be at high risk for morbidity and mortality despite the effectiveness of the antiretroviral drugs in reducing the viral load; residual inflammation being one of the factors responsible for the immunopathogenesis[4], further compounded by non-adherence or interruption in the treatment regimen in the Indian settings and other developing nations.

Attention has been focused on the antiviral activities of various proteinase inhibitors, because many viruses including HIV-1 require proteolytic cleavage, which can be specifically inhibited by proteinase inhibitors, to become mature and infectious[5,6]. Bjorck *et al*[7] reported that human cystatin C, a thiol proteinase inhibitor, blocks replication of herpes simplex virus (HSV) *in vitro*, suggesting an important role of thiol proteinase in the maturation process of the virus. In another study, recombinant human cystatin C was demonstrated to be a potent inhibitor of replication of human coronaviruses[8]. Cystatins function as reversible, tight-binding inhibitors of cysteine proteases, and generally do not possess specific inhibitory activity to particular cathepsins. Cystatins exert several immunomodulatory functions by controlling the activity of cysteine proteases or by other mechanisms not related to their inhibitory function[9,10]. A broad spectrum of biological roles has been suggested for cystatins, including a role in protein catabolism, regulation of hormone processing and bone resorption, inflammation, antigen presentation and T-cell dependent immune response as well as resistance to various bacterial and viral infections[10].

Cystatin C is a low molecular weight protein that is constitutively produced by all nucleated cells of the body and freely filtered by glomeruli. Serum cystatin C is not only a sensitive marker for renal dysfunction, but also a potential marker for inflammation, suggesting thereby that this marker may be associated with other pathological conditions as well. In population-based studies, cystatin C levels, or cystatin C-based glomerular filtration rate (GFR) estimates emerged as efficient predictors of cardiovascular disease outcomes, and as potential biomarker for endovascular dysfunction in HIV disease[11]. In these studies, cystatin C levels were also correlated with several markers of inflammation [including plasma C reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and fibrinogen]. A 3-year prospective cohort study was conducted among men under good infection control with HAART to test the impact of elevated serum cystatin C on the development of cancers, and cystatin C elevation emerged as a risk factor for cancer in these patients[12]. The findings suggested that monitoring of serum cystatin C level may enable earlier recognition of cancers in subjects with HIV infection[12].

Cystatin C is abundantly present in the human seminal plasma. In this issue, Vernekar *et al*[13] have reported anti-HIV activity of cystatin C derived from human seminal plasma and purified for the study. They showed the interaction of cystatin C with the different HIV-1 proteins gp160, gp120, p31 and p24 and its inhibitory effect on HIV-1 protease activity suggesting that it may prevent the normal functioning of HIV protease which in turn, would potentially prevent viral replication and transmission. Further, using the TZM-bl reporter cell line, they demonstrated the dose dependent inhibitory effect of cystatin C on HIV-1 infectivity in the cells. The authors conclude that cystatin C may serve as a potential candidate microbicide to prevent replication of sexually transmitted HIV-1, and when used in combination with the antiretroviral drugs, can effectively reduce viral load[13].

In an earlier study, Yoshii *et al*[14] demonstrated that inhibition of cathepsin B activity by cystatin C expression or by a specific inhibitor for cathepsin B, significantly enhanced the CD4-independent HIV-1 vector infection in HeLa and TE671 cells, both of which expressed cathepsin B at relatively higher levels. Their study suggests that cathepsin B inhibits CD4-independent HIV-1 infection. The CD4-independent HIV-1 infection occurs through acidic endosomes. The HIV-1 particles are degraded predominantly by cathepsin B after the viral particles are internalized into endosomes, reducing the CD4-independent infection. Additionally, in this study, it is speculated that the CD4-dependent HIV-1 entry in the host cells does not occur through acidic endosomes. Even when the CD4-dependent HIV-1 particles are internalized to endosomes, the viral entry may occur before the HIV-1 virion-containing endosomes become acidic.

Cystatin C needs to be evaluated in future for its effect on HIV-1 variants that are either CD4 dependent and CD4 independent for infecting cells, to determine whether the antiviral effects of cystatin C are restricted to CD4 dependent HIV alone or otherwise. Also, the inhibitory effect of cystatin C should be checked for the various viral strains to determine its role as an effective antiviral agent that may be used in combination with antiretroviral therapy.

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