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Inhibiting Protease Auto-processing: A Novel Strategy for Anti-HIV-1 Drug Development

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HIV (Human Immunodeficiency Virus) is a lentivirus that causes Acquired Immunodeficiency Syndrome (AIDS) [1], an infectious disease, in which gradually failure of human immune system leads to life-threatening opportunistic infections and cancers. Since the discovery of HIV-1 in 1981, AIDS has killed more than 25 million people. In addition, there are an estimated 34 million people living with HIV worldwide; among them, millions have developed AIDS [2]. HIV/AIDS is one of the leading causes of adult deaths in the developing world.

HIV-1 protease (PR) is retroviral aspartyl proteases, the virus-encoded enzyme that is essential for the viral life-cycle [3,4]. It exists as a stable homodimer, and the active site is formed at the dimer interface by two aspartic acids, each contributed by one monomer [5,6]. In the HIV-1 infected cell, HIV protease is initially synthesized as part of the Gag-Pol precursor [1,4]. HIV protease recognizes and cleaves newly synthesized Gag and Gag-Pol polyproteins, at least 10 specific sites, releasing the structural proteins components and enzymes for infectious viral particles [7-9]. The immature protease embedded in the Gag-Pol precursor has intrinsic, but limited proteolytic activity [10,11]; it is capable of processing certain cleavage sites [12], but not other sites. It catalyzes the cleavage reactions that lead to liberation of mature fully active protease-a process defined as protease autoprocessing [10].

In the last decades, much effort has gone into investigations of mature protease and hundreds of mature protease structures have been solved. Structure-guided rational design has been enormously successful for the development of mature protease inhibitors. Currently, there are ten FDA approved HIV-1 protease inhibitors for clinical applications: amprenavir (APV, Agenerase), atazanavir (ATZ, Reyataz), darunavir (TMC114, Prezista), fosamprenavir (Lexiva), indinavir (IDV, Crixivan), lopinavir (LPV), nelfinavir (NFV, Viracept), ritonavir (RTV, Norvir), saquinavir (SQV, Fortovase/Invirase), and tipranavir (TPV, Aptivus). These inhibitors, however, all belong to the same mechanistic class, in that they are designed to bind the active site of mature protease. The drug resistant HIV-1 strain that is resistant to one or more PIs likely increase due to this single mode of inhibition [13]. Hence, new inhibitors with different action mechanisms to interfere with protease function are needed.

In contrast, HIV protease auto processing has not been previously investigated for anti-HIV drug development. The major barrier is that the molecular and cellular mechanisms regulating protease auto processing are poorly understood, and detailed information regarding the structural conformation of the immature protease is not available. It has long been assumed that the immature protease needs to fold into a conformation, similar to that observed for the mature protease, to execute proteolysis function. However, recent studies demonstrated that the immature protease is much less sensitive to the current protease inhibitor than the mature protease, even though their amino acid sequence is identical [14-16]. It suggests that these two forms of HIV-1 protease are structurally different. Thus, searching novel inhibitors that have stronger affinity to the immature protease to block autoprocessing would be an alternative new approach to overcome drug resistance.

Since structure-based design for autoprocessing inhibitor is impractical, a cell based functional assay may provide a useful alternative strategy. Recently, a mammalian cell based simple model system has been reported for protease autoprocessing analysis [14,17]. This simplified system employs a GST fusion protease mini precursor that mimics the proviral system; it allows examination of protease autoprocessing in the context of live cells; importantly, it is sensitive for quantification of protease autoprocessing by directly monitoring amounts of the fusion precursor and autoprocessing products. This makes it possible for isolation of potential autoprocessing inhibitors through functional screening of small molecule compounds.

Further, protease inhibitors developed from a structure-based strategy only target active site of mature protease, and are often associated with strong side effects such as cytotoxicity [18]. In contrast, drugs derived from a cell based system may target multiple sites/stages that block protease autoprocessing. For example, charge properties of a surface residue H69 impedes protease autoprocessing [19], and the H69E inhibitory effect on protease autoprocessing is modulated by cysteine 95, as well as other residues [20], suggesting that protease autoprocessing can be regulated by residues outside the catalytic site. Therefore, these residues may serve as a direct target of autoprocessing inhibitor. Furthermore, a cell-based system is anticipated to eliminate molecules that have strong cytotoxicity at the very beginning of screening [20].

Together, protease autoprocessing becomes a potential target for identification of anti-HIV-1 inhibitors. Drugs that inhibit immature protease from autoprocessing will provide a mode of HIV-1 inhibition that is distinct from the current protease inhibitors, and will complement the current protease inhibitors.

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