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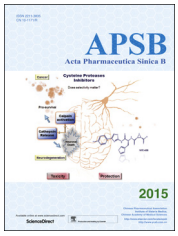

REVIEW

Pharmacological intervention of HIV-1 maturation

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KEY WORDS

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Abstract Despite significant advances in antiretroviral therapy, increasing drug resistance and toxicities observed among many of the current approved human immunodeficiency virus (HIV) drugs indicate a need for discovery and development of potent and safe antivirals with a novel mechanism of action. Maturation inhibitors (MIs) represent one such new class of HIV therapies. MIs inhibit a late step in the HIV-1 Gag processing cascade, causing defective core condensation and the release of non-infectious virus particles from infected cells, thus blocking the spread of the infection to new cells. Clinical proof-of-concept for the MIs was established with betulinic acid derived bevirimat, the prototype HIV-1 MI. Despite the discontinuation of its further clinical development in 2010 due to a lack of uniform patient response caused by naturally occurring drug resistance Gag polymorphisms, several second-generation MIs with improved activity against viruses exhibiting Gag polymorphism mediated resistance have been recently discovered and are under clinical evaluation in HIV/AID patients. In this review, current understanding of HIV-1 MIs is described and recent progress made toward elucidating the mechanism of action, target identification and development of second-generation MIs is reviewed.

Abbreviations: BMS, Bristol-Myers Squibb; CA, capsid; GSK, GlaxoSmithKline; HIV, human immunodeficiency virus; MA, matrix; MI, maturation inhibitor; PR, protease; PI, protease inhibitor; SIV, Simian immunodeficiency virus; SP1, spacer protein 1

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1. Introduction

HIV-1 maturation is the final step of the virus lifecycle. It involves two coupled and highly regulated events: immature virus particle release driven by the viral Gag protein and a proteolytic cleavage cascade directed by the viral protease (PR). Numerous studies have shown that maturation is essential for HIV-1 infectivity because genetic mutations either in Gag or PR that inhibit maturation lead to the production of non-infectious HIV-1 particles[1–7]. Pharmacological intervention in HIV-1 maturation has been successfully explored, resulting in the discovery and development of two classes of HIV-1 inhibitors. One class of inhibitors, the PR inhibitors (PI), target and inhibit the enzymatic activity of the HIV-1 PR. This class has 9 FDA-approved inhibitors that are currently used in treating AIDS patients worldwide. Another class of inhibitors currently under clinical development binds the Gag substrate and specifically blocks PR-mediated Gag cleavage. The compounds that disrupt the Gag cleavage are designated the maturation inhibitors (MIs) in a way to differentiate them from the PI.

The first-in-class MI is bevirimat, also known as 3-*O*-(3′,3′-dimethylsuccinyl) betulinic acid, PA-457, or MPC-4326 (Fig. 1)[8–10]. Bevirimat specifically inhibits a specific step in Gag processing: cleavage of the CA-spacer protein 1 (SP1) intermediate that occurs late in the Gag cleavage cascade (Figs. 2 and 3). Despite promising data in a phase IIa clinical trial, further development of bevirimat was suspended in 2010 due to bevirimat-resistance conferring Gag SP1 polymorphisms present in approximately 50% of HIV-1-infected patients[11].

Considering that a number of review articles on bevirimat, the prototype HIV-1 MI, have been published[12–14], the purpose of this review is to describe what is known about the HIV-1 MIs with particular reference to those advances recently made in the mechanisms of action, target identification and discovery and clinical development of new generation MIs highly effective against bevirimat-resistant viruses.

2. HIV-1 assembly and maturation

In HIV-1 lifecycle, the Gag precursor protein $Pr55^{Gag}$ drives the final stage of viral replication: assembly and maturation. Following synthesis, $Pr55^{Gag}$ is transported to the plasma membrane where virus assembly occurs. Through a complex combination of Gag–lipid, Gag–Gag, and Gag–RNA interactions, a multimeric budding structure forms at the inner leaflet of the plasma membrane. The budding virus particle is ultimately released from the cell surface in a process that is promoted by an interaction between the late domain in the p6 region of Gag and host proteins, most notably the endosomal sorting factor *TSG101* (tumor susceptibility gene 101). As illustrated in Fig. 2, concomitant with particle release, the viral

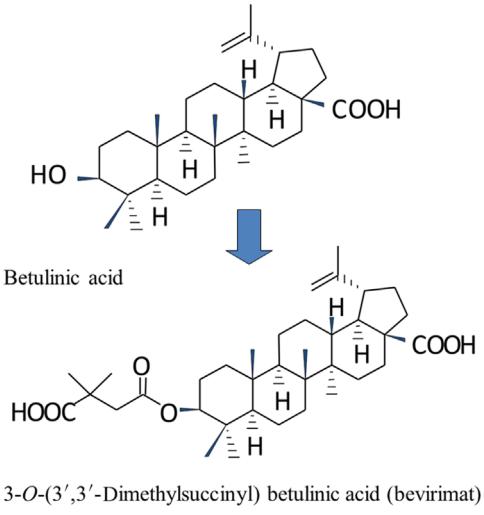

Figure 1 The chemical structures of betulinic acid (top panel) and its derivative bevirimat, 3-*O*-(3′,3′-dimethylsuccinyl) betulinic acid (bottom panel).

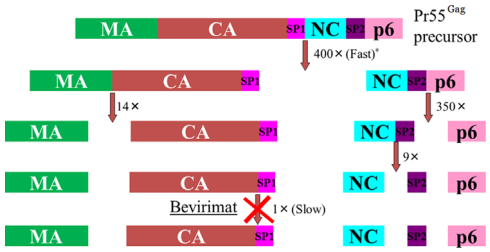

Figure 2 The processing cascade of HIV-1 Gag polyprotein precursor. The proteolytic cleavage of HIV-1 Gag polyprotein precursor *via* the viral protease is a sequential and high-order event. The numbers indicated underneath the various precursors show the cleavage rates of each individual cleavage step relative to that of CA-SP1 precursor cleavage, the final step with the slowest rate of cleavage in the Gag processing cascade. CA-SP1 cleavage is a primary target of the HIV-1 maturation inhibitor bevirimat.

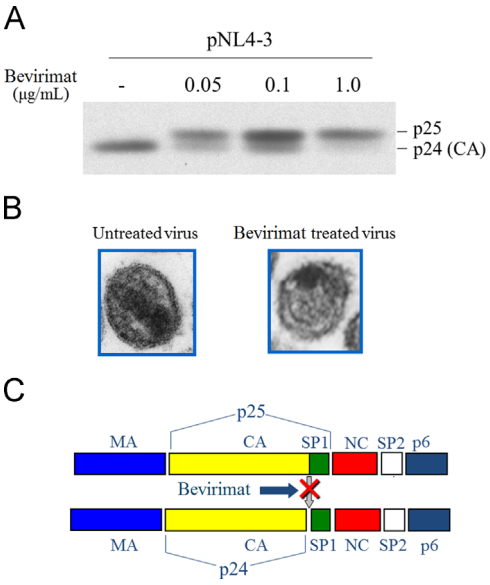

Figure 3 Mechanism of action of HIV-1 maturation inhibitor Bevirimat. In panel A, HeLa cells were transfected with pNL4-3 and cultured in the absence or presence of indicated concentrations of bevirimat. Two days posttransfection, cells were metabolically labeled for 2 h with [^{35}S]Met/Cys. Virus lysates were immunoprecipitated with anti-HIV antibody. The positions of virally encoded proteins p25 and p24 are indicated. Note the accumulation of p25 in the presence of bevirimat. Panel B is the thin section electron microscope analysis of virions produced from bevirimat-treated or -untreated HeLa cells following transfection with pNL4-3 proviral DNA plasmid. Panel C schematically shows that bevirimat disrupts the CA-SP1 cleavage and blocks the release of mature CA protein.