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Review

Molecular recognition in the human immunodeficiency virus capsid and antiviral design

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ABSTRACT

Many compounds able to interfere with HIV-1 infection have been identified; some 25 of them have been approved for clinical use. Current anti-HIV-1 therapy involves the use of drug cocktails, which reduces the probability of virus escape. However, many issues remain, including drug toxicity and the emergence of drug-resistant mutant viruses, even in treated patients. Therefore, there is a constant need for the development of new anti-HIV-1 agents targeting other molecules in the viral cycle. The capsid protein CA plays a key role in many molecular recognition events during HIV-1 morphogenesis and uncoating, and is eliciting increased interest as a promising target for antiviral intervention. This article provides a structure-based, integrated review on the CA-binding small molecules and peptides identified to date, and their effects on virus capsid assembly and stability, with emphasis on recent results not previously reviewed. As a complement, we present novel experimental results on the development and proof-of-concept application of a combinatorial approach to study molecular recognition in CA and its inhibition by peptide compounds.

Contents

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1. Introduction

The biological cycle of any virus involves a complex chain of molecular recognition events between viral proteins and nucleic acids, and between viral and cellular macromolecules. In principle, any small molecule capable of interfering with any one of those reactions constitutes a potential antiviral drug. Thus, many targets and strategies for antiviral intervention exist (De Clercq, 2002; Kräusslich and Bartenschlager, 2009); most of them are essentially unexplored.

Human immunodeficiency virus type 1 (HIV-1) has been the major target of antiviral research to date. Many compounds able to interfere with HIV-1 infection have been identified; some 25 of them have been approved for clinical use, and others are in clinical trials (De Clercq, 2004; Broder, 2010; Ghosh et al., 2011). Life expectancy for acquired immunodeficiency syndrome (AIDS) patients was extremely short before the first antiretroviral drug, zidovudine, was introduced in 1987. Still, administering a single drug soon proved inadequate, due to the frequent emergence in the patients of drug-resistant virus variants. HIV-1 and other RNA virus populations are quasispecies formed by non-identical individuals that result from error-prone replication, and may evolve very rapidly (Domingo, 1989; Domingo et al., 2001). High mutation frequencies, high replication rates and large population sizes lead together to a high probability of finding in an infected host one or more individual viruses that carry the mutation (or combination of mutations) required to escape from the action of a single antiviral drug.

Current highly active antiretroviral therapies (HAART) (Barbaro et al., 2005) involve the use of cocktails of (usually) three anti-HIV-1 drugs. HAART reduces drastically the probability of virus escape because enough mutations must accumulate in a single virus genome to impair the action of different drugs that act through different mechanisms on different targets. Introduction of HAART around 1996 was decisive in turning HIV-1 infection from a lethal disease into a chronic disease with long life expectancy and improved quality of life for patients receiving adequate treatment. However, many critical issues still remain, including drug toxicity, poor patient compliance, and the emergence of drug-resistant virus variants, even in HAART-treated patients. Therefore, there is a constant need for new anti-HIV-1 drugs targeting other molecules and molecular recognition events in the viral cycle.

Most of the approved anti-HIV drugs target the HIV-1 enzymes reverse transcriptase (RT) or protease (PR). A few are directed against the HIV-1 integrase (IN), virus entry (by targeting either receptor/coreceptor recognition or membrane fusion; Melby and Westby, 2009), or virion maturation (Salzwedel et al., 2007; Adamson et al., 2009). The structural proteins nucleocapsid (NC) and capsid (CA) are, however, eliciting increased interest as promising targets for anti-HIV-1 intervention. Interest in NC and CA for antiviral research has been greatly stimulated by recent advances in the understanding of nucleocapsid and capsid structure and