Review paper

CURRENT APPROACHES TO ANTI-HIV-1 THERAPY

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SUMMARY

The acronym AIDS ("acquired immunodeficiency syndrome") has become the symbol for one of the biggest challenges to medicine in the 20th century. Already 2 years after the first reports on patients suffering from Kaposi's sarcoma or Pneumocystis carinii pneumonia a human retrovirus was identified as the infectious cause for AIDS. This retrovirus, now known as human immunodeficiency virus type 1 (HIV-1), has been the target of a combined effort of biological, medical and pharmacological research over the past decade. Whereas many different antiretroviral therapeutic strategies are currently still tested in laboratories or in clinical trials, some anti-HIV-1 drugs have already made their way to clinical routine application.

KEY WORDS

HIV-1, AIDS, antiretroviral treatment, nucleoside analogs

INTRODUCTION

All possible approaches to anti-HIV-1 therapy have to take into account the complex life cycle of lentiviruses as depicted in the figure 1. Every single step of the HIV-1 life cycle, from attachment of the virion to the membrane of target cells to the budding and release of new infectious virus, represents a possible target for therapeutic intervention. Whereas avian and lower vertebrate retroviruses produce only structural proteins, HIV-1 possesses also transregulating proteins which are able to modulate expression of the virus (1).

ANTIRETROVIRAL STRATEGIES

Of all conceivable antiretroviral strategies, the most successful will fight the virus before it reaches the nucleus of the infected cell. Besides blocking of receptor binding and virus uptake, the disturbance of the synthesis of the DNA provirus by the reverse transcriptase (RT) is still one of the most promising approaches. Because the RT is not a cellular enzyme, it is conceivable to target it without impairing vital functions within the cell. Two types of substances have emerged over the past decade as most promising candidates: nucleoside analogs and non-nucleoside RT inhibitors (2,3).

a. Nucleoside analogs.

Dideoxynucleosides are identical to deoxynucleosides, except for a critical side chain. Like deoxynucleosides they are taken up into the cells and are phosphorylated