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GENERAL REVIEW

Understanding HIV infection for the design of a therapeutic vaccine. Part I: Epidemiology and pathogenesis of HIV infection

Comprendre l'infection par VIH dans l'objectif d'un vaccin thérapeutique. Première partie : épidémiologie et pathogenèse de l'infection par le VIH

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Summary HIV infection leads to a gradual loss $CD4^+$ T lymphocytes comprising immune competence and progression to AIDS. Effective treatment with combined antiretroviral drugs (cART) decreases viral load below detectable levels but is not able to eliminate the virus from the body. The success of cART is frustrated by the requirement of expensive life-long adherence, accumulating drug toxicities and chronic immune activation resulting in increased risk of several non-AIDS disorders, even when viral replication is suppressed. Therefore there is a strong need for therapeutic strategies as an alternative to cART. Immunotherapy, or therapeutic vaccination, aims to increase existing immune responses against HIV or induce de novo immune responses. These immune responses should provide a functional cure by controlling viral replication and preventing disease progression in the absence of cART. The key difficulty in the development of an HIV vaccine is our ignorance of the immune responses that control of viral replication, and thus how these responses can be elicited and how they can be monitored. Part one of this review provides an extensive overview of the (patho-) physiology of HIV infection. It describes

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the structure and replication cycle of HIV, the epidemiology and pathogenesis of HIV infection and the innate and adaptive immune responses against HIV. Part two of this review discusses therapeutic options for HIV. Prevention modalities and antiretroviral therapy are briefly touched upon, after which an extensive overview on vaccination strategies for HIV is provided, including the choice of immunogens and delivery strategies.

MOTS CLÉS
VIH-1 ;
Thérapie immunitaire ;
Vaccin ;
Thérapie antirétrovirale ;
Vecteur ;
Cellule dendritique

Résumé L'infection par le VIH provoque une perte graduelle des cellules T CD4, compromettant la compétence immunitaire et aboutissant au SIDA. Un traitement efficace avec combinaison d'antirétroviraux (cART) diminue le taux viral plasmatique sous le seuil de détection, sans pour autant éliminer le virus complètement de l'organisme. Cependant, le succès en demi-teinte du cART s'explique par le coût onéreux des traitements, qui doivent être dispensés à vie, la toxicité cumulative des médicaments et l'activation chronique du système immunitaire, augmentant les risques de comorbidités, cela même sans réplication virale détectable. Ainsi, il est crucial de développer des stratégies thérapeutiques alternatives au cART. L'immunothérapie, ou vaccination thérapeutique, a pour objectif d'augmenter l'immunité existante contre le VIH et/ou d'induire une immunité première. Ces réponses immunitaires devraient fournir une cure fonctionnelle en supprimant la réplication virale et en enrayant la progression de la maladie en absence de cART. Cependant, nos lacunes de connaissance sur les réponses immunitaires qui contrôlent la réplication du VIH et des mécanismes par lesquels elles sont induites et détectées mettent un frein au développement d'un vaccin contre le VIH. Cette revue décrit dans un premier temps la structure du VIH, la réplication virale et l'évolution clinique après infection par le VIH. Les réponses immunitaires innées et adaptatives contre le VIH sont contrées par l'activation généralisée, l'épuisement du système immunitaire et l'échappement du virus à l'immunité spécifique. Les modalités de prévention et de thérapie antirétrovirale sont également traitées brièvement. Ensuite, une vue d'ensemble approfondie des stratégies de vaccination thérapeutique contre le VIH est détaillée, ainsi qu'une discussion sur le choix de l'immunogène et les stratégies d'administration.

Human immunodeficiency viruses

HIV is a lentivirus belonging to the family of Retroviridae, causing acquired immunodeficiency syndrome (AIDS). Retroviruses are enveloped viruses using reverse transcription of viral RNA into DNA during replication [1]. AIDS is caused by two closely related but distinct types of HIV: HIV-1 and HIV-2. Both HIVs originate from multiple cross-species transmissions of simian immunodeficiency viruses (SIV) that naturally infect African primates. Zoonotic transfers gave rise to viruses that could spread in humans. The HIV-2 lentivirus originates from the transmission of SIV from sooty mangabey to humans [2]. The majority of HIV-2 infections have been found in West Africa and, with lower prevalence rates in countries with historical and socio-economic ties such as Portugal, France, Brasil, India and the United States [2,3]. The considerably more virulent HIV-1 originates from the transfer of SIV from the chimpanzee to humans [4] and shows marked genetic variability. The pandemic form of HIV-1, also called the main (M) group is the major cause of AIDS. The other three HIV-1 lineages, termed group N, O and P are considerably less prevalent than group M. Each lineage results from an independent cross-species transmission event [5]. Group M is genetically further diversified into subtypes or clades designated by letters A to K. In different parts of the world, different subtypes of HIV-1 predominate [6]. Subtype B is the most common form in West and Central Europe, Australia, North and South America, and several Southeast Asian countries, northern Africa and the Middle East. The epidemic global spread of HIV-1 began in the late 1970s. By the end of 1981, a total of 270 cases of severe immunodeficiency among gay men were reported and a year later the term AIDS was formally established [7].

Epidemiology

HIV attacks the body's immune system and without effective treatment the immune system is weakened to a stage where opportunistic infections and other illnesses occur, causing acquired immunodeficiency syndrome (AIDS). The number of individuals living with HIV or AIDS continues to grow but the incidence of new HIV infection is nowadays increasing more slowly in many regions of the world. In eastern Europe and in Asia, the incidence of HIV infections is rising faster than in the rest of the world. In 2012, 35.3 million individuals were infected with HIV worldwide, including 2.3 million new cases, and more than 1.6 million deaths were related to AIDS [8]. Hence HIV/AIDS is the leading infectious cause of adult death in the world today and also fuels other epidemics of global concern, most notably opportunistic infectious diseases such as tuberculosis [8].

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