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GENERAL REVIEW

Understanding HIV infection for the design of a therapeutic vaccine. Part II: Vaccination strategies for HIV

Comprendre l'infection par VIH dans l'objectif d'un vaccin thérapeutique. Deuxième partie : stratégies de vaccination contre 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 lifelong 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 drogues 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 adaptives 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.

Prevention modalities and therapeutic intervention for HIV

Modalities to reduce infection rates and transmission

In the era of a persisting HIV/AIDS epidemic and the absence of an effective HIV vaccine, there is a high need for effective prevention strategies to constrain the spread of HIV. In order to achieve high impact prevention, behavioral, biomedical and structural interventions must be combined and tailored to the target population [1,2]. Behavioral strategies include condom usage, sexual abstinence, HIV counseling and testing and monogamy for sexual transmission and the use of safe injection equipment for intravenous drug use. These strategies have been shown necessary, but not sufficient to reduce HIV transmission or acquisition rates, and are hard to maintain [2]. For an effective prevention approach, behavioral strategies should be combined with structural interventions for the social, political, economic and environmental context in which behavior occurs, and with biomedical interventions. Regarding the latter, male circumcision was one of the first tools proposed for prevention of HIV acquisition [2]. Later on, preexposure prophylaxis (PrEP) with antiretroviral drugs was added to the prevention toolkit. These drugs can either be administered orally, or topically as vaginal microbicides providing a female-initiated method for PrEP. Antiretroviral drugs can also be applied after either occupational or nonoccupational exposure to HIV as postexposure prophylaxis (PEP). The reduction in viral load as a result of antiretroviral therapy in individuals, who tested positive for HIV, reduces infectiousness and thus helps to reduce transmission as secondary prevention [3]. As discussed above, STIs increase the risk of HIV transmission and therefore, STI treatment-interventions are included in HIV prevention approaches [2].

Antiretroviral treatment, benefits and limitations

Antiretroviral drugs form the cornerstone of medical management of HIV-1 infection. Administration of a cocktail of at least three HIV-1 specific antiviral drugs, also known as highly active antiretroviral therapy (HAART) or combination antiretroviral therapy (cART), has dramatically reduced AIDS-related mortality and morbidity. The use of cART suppresses viral replication to undetectable levels in plasma and a steady recovery of $CD4^+$ T-cells is achieved [4]. Antiretroviral drugs can be divided into six classes based on their mechanism of action on the HIV-1 replication cycle (Fig. 1). The first step of the replication cycle, viral entry, is targeted by fusion inhibitors and by antagonists of CCR5.

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