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Langerhans cells and dendritic cells in innate defense against pathogens

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Summary for laymen

Introduction

Every day the body is exposed to a large array of potential disease-causing pathogens. Most of the time, we do not get ill: the skin and mucosal tissues form an important barrier that prevents invading pathogens from entering the body. At the time that pathogens cross this barrier, the immune system becomes activated to clear the invading pathogen. The immune system consists of an advanced interplay of different cell types, where the dendritic cell (DC) plays an important role. DCs are located in the skin and mucosal tissues and recognize foreign structures, such as viruses, bacteria, and fungi. These are recognized via a large array of receptors on the cell surface that act as tentacles to screen the surrounding environment. After recognizing the pathogen, DCs become activated and migrate from the tissues to the lymph nodes. The lymph node contains many T cells (white blood cells), which are instructed by the DCs to expand and become activated. This is one of the reasons why our glands feel swollen when we have a cold or a sore throat. The activated T cells subsequently return to the site of infection and remove the invading pathogen. After a time of rest, we recover from the infection. Often B cells (white blood cells) also establish a memory, such as in the case of the Measles Virus. This way the body will respond quickly when the same pathogen is encountered for the second time, eradicating the pathogen before it causes damage.

However, at times we do get ill. Many pathogens have found ways to enter the body and escape from the immune system, mislead the immune system, or use the immune system to their own advantage. How this process is mediated is not completely clear and varies among pathogens. Since DCs play a central role in the induction of the immune system, they form a potential target for pathogens to invade the body and evade the immune system.

In the skin and mucosal tissues, several subsets of DCs are present. These can be distinguished by the receptors present on the cell surface. In the epidermis, the top layer, Langerhans cells (LCs) are present. Discovered and named after Paul Langerhans, these cells express the receptor Langerin. In the layer below, the dermis, sub-epithelial DCs are present and these cells express, amongst other molecules, the receptor DC-SIGN (Figure 1, page 217).

Research question

During my PhD project, I have investigated the interaction between pathogens and DCs. I have focussed on the role of Langerhans cells and sub-epithelial DCs in the dissemination of pathogens within the body. I have examined *Borrelia burgdorferi*, causative agent of Lyme disease, herpes simplex virus (HSV), and HIV.

Results

Borrelia burgdorferi and Lyme disease

Borrelia, the causative agent of Lyme disease, is a bacteria that infects humans and animals and is transmitted via the saliva of ticks. While feeding on a host, ticks can introduce *Borrelia* into the host's skin where *Borrelia* encounters DCs. The saliva contains an array of molecules that facilitate feeding of the tick. In chapter 10, we investigated the effect of a specific salivary protein on host-defense response. We demonstrate that in the presence of tick saliva, DC activation is impaired and subsequently the host's T cell response is inhibited. This allows *Borrelia* to disseminate throughout the body. The receptor DC-SIGN on sub-epithelial DCs plays an important role.

This information not only provides a better understanding of the interaction between host (human) and tick and the molecules involved, it also enhances our understanding of the immune- evading mechanisms used by *Borrelia*. In addition, this knowledge can contribute to the development of novel anti-inflammatory and immune-suppressive agents for diseases such as rheumatoid arthritis.

Herpes simplex virus and the cold sore

Herpes simplex virus (HSV) is the causative agent of the cold sore and genital herpes. Characteristically, after entering the body, this virus will remain in the body without being eradicated by the immune system. This is also known as 'latency'. Once the immune system is sub-optimal, for example through a lack of sleep, exposure to UV light, or a common cold, the virus reactivates and the cold sore appears on the lip. Via (indirect) contact with an infected individual with a cold sore, such as kissing or drinking from the same cup, the virus can be transmitted to another person. Cells in our lips are easily infected with HSV; however, DCs are also present here. In chapter 8, we investigated the role of DC-SIGN on sub-epithelial DCs in the transmission of HSV within the host. We demonstrate that DC-SIGN enhances HSV infection of DCs; in addition, DC-SIGN enhances transmission of HSV from one cell to another. This provides a mechanism for HSV to facilitate dissemination throughout the body.

HIV and how it enters the body

HIV is mainly transmitted via sexual and blood contact. HIV infects primarily white blood cells (T cells) that are largely present in the lymph nodes. There is a relatively large distance between the site of infection, genital mucosa, and the T cells in the lymph nodes. Therefore, HIV is captured by DC-SIGN on sub-epithelial DCs and 'hijacks' the DCs to migrate to the lymph node where it encounters a large amount of T cells. Subsequently, an infection is established. With this knowledge, it is plausible that preventing DC-SIGN interaction with HIV could decrease the dissemination of HIV within the body. In chapters 6 and 7, we demonstrate that naturally-occurring proteins, such as MUC1 in human milk and a protein derived from a nematode, prevent HIV binding to DC-SIGN. Ideally, these compounds could be included in a genital cream, which decreases HIV infection.

Studies have shown that compared to other viruses, HIV is not very infectious. My colleague Lot de Witte, has demonstrated that LCs provide a protective barrier against HIV infection. LCs express the receptor Langerin, which binds HIV and subsequently targets it for degradation. Thus LCs protect against HIV, while sub-epithelial DCs enhance HIV infection. In the development of genital creams, it is important to maintain Langerin function, while DC-SIGN binding to HIV should be prevented. Remarkably, Langerin and DC-SIGN are partly homologous and interact with similar structures. This hampers the design of genital microbicides.

In chapter 5 we have used a model to screen potential structures for the interaction with Langerin. In addition, we make a suggestion for a structure that does prevent HIV infection via DC-SIGN on sub-epithelial DCs, without interfering with Langerin.

STDs and HIV acquisition

Sexual transmitted diseases (STDs) enhance the risk to acquire HIV. Several hypotheses have been proposed. STDs can damage the mucosa and cause inflammation. This facilitates HIV entry and allows interaction with DC-SIGN on sub-epithelial DCs, which facilitates HIV dissemination. In addition, T cells, which are a target for HIV infection, are attracted to the site of infection.

In this thesis I have investigated whether LCs lining the mucosa are altered in the presence of STDs caused by a bacteria or fungi, and whether this has consequences for the protective function of LCs in HIV infection. In chapter 3, we demonstrate that in the presence of STDs, LCs are altered and lose their protective function. LCs themselves are infected with HIV and start to produce viral progeny. In addition, LCs become very efficient in transmitting HIV to target cells, such as T cells, in the presence of an STD. This provides an explanation for why there is an enhanced risk to acquire HIV in the presence of an STD, even when there is no obvious damage of the mucosa.

HSV is an STD that causes genital herpes, which manifest as blisters in the genital tissues. Thus far, little is known about the consequences of HSV infection of LCs. In chapter 4, we demonstrate that LCs are productively infected with HSV. The presence of HSV also has consequences for the susceptibility to HIV infection. In the presence of HSV, LCs are altered and are more readily infected with HIV and new viral HIV particles are produced. This provides a mechanism for HSV to make the host more susceptible to HIV infection.

Together, this research demonstrates that LCs form a protective barrier against HIV infection. However, in the presence of an STD, LCs lose their protective function and are both efficiently infected with HIV and efficiently transmit HIV to target cells. This research emphasizes the need for prevention and early detection of STDs to limit the chance to acquire HIV.

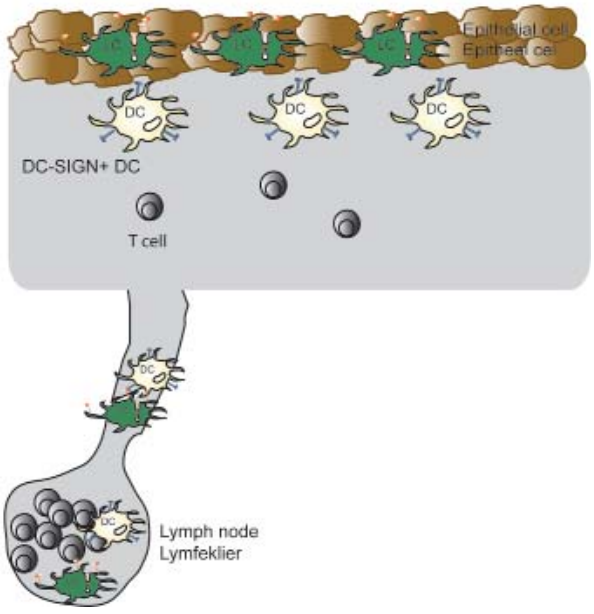
General implications

In this thesis, the interaction between pathogens and DC subsets was investigated. I have demonstrated that a plethora of pathogens interact with DC-SIGN on sub-epithelial DCs to facilitate infection of and dissemination throughout the host. On the other hand, Langerin on LCs has a different function in the interaction with pathogens. This knowledge can contribute to the development of new therapies against pathogens.

In addition, the studies described in this thesis contribute to the general immunological knowledge of DCs. This knowledge can be of use in the development of new therapies for diseases that either are a result of a lack of immune activation, such as cancer, or an over-reactive immune system, such as auto-immune diseases, allergies, and rheumatoid arthritis.

LCs were discovered more than a hundred years ago. However, we are still only at the beginning of unravelling the immunological function of these cells. I hope that my thesis can contribute to the knowledge of the immunological and virological function of DCs, as well as the development of protective vaccines and successful therapies.

Figure 1. Schematic overview of dendritic cells in the skin and mucosal tissues. In the top-layer, which is in constant contact with the environment, Langerhans cells (LCs, green) are surrounded by epithelial cells (brown). In the lower layer, sub-epithelial dendritic cells are present (DCs, yellow). LCs express the receptor Langerin on their surface, while sub-epithelial DCs can be distinguished by the expression of DC-SIGN. LCs and DCs screen their surrounding for invading pathogens. Upon detection of a pathogen, LCs and DCs migrate from the tissues to the lymph nodes. In the lymph nodes, T cells are instructed by the LCs and DCs to eradicate the invading pathogen.



Figuur 1. Schematische tekening van de dendritische cellen in de huid en slijmvliezen. In de bovenste laag die in contact staat met de buitenwereld bevinden zich naast de steuncellen (epitheel cellen, bruin) de Langerhans cellen (LCs, groen). In de laag eronder bevinden zich (onder andere) sub-epitheliale dendritische cellen (DCs, geel). LCs hebben de receptor Langerin op hun oppervlakte terwijl sub-epitheliale dendritische cellen DC-SIGN op hun oppervlakte hebben. LCs en DCs herkennen inkomende ziekteverwekkers waarna ze zich verplaatsen naar de lymfeklieren. In de lymfeklier bevinden zich veel witte bloed cellen (T-cellen) die de ziekteverwekkers vervolgens onschadelijk maken.