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KSHV interaction with Langerhans and dermal dendritic cells through C-type lectins

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The skin contains two types of dendritic cells (DC), Langerhans cells (LC), which reside in the epidermis in close contact with keratinocytes, and dermal dendritic cells (DDC), resident in the dermis. LC and DDC process cutaneous antigens and migrate out of the skin into the draining lymph nodes to present antigens to T and B cells. Recent reports showed that LC and DDC play an important role in certain virus infections, such as HIV-1 and HSV. Because of the strategic position of LC and DDC at mucosal sites of infection and the ability of these cells to capture pathogens, we hypothesized that these cells could be infected with KSHV and have an important role in the development of Kaposi's sarcoma. We have previously shown that KSHV enters monocyte-derived dendritic cells (MoDC) through DC-SIGN, resulting in a nonproductive infection. We have now generated LC and DDC from pluripotent cord blood CD34+ precursors by culture with GM-CSF, TNF, and TGF-B to obtain LC, and GM-CSF, TNF, and IL4 to generate DDC. These expressed the typical phenotype of LC, i.e., CD207 ^{pos}, CD14^{pos}, CD11b ^{neg}, CD1a^{pos}, HLA-DR^{pos}, DC-SIGN ^{neg}, and dermal DC, i.e., DC-SIGN^{pos}, CD14 ^{neg}, CD11b^{pos}, CD1a^{pos}, HLA-DR^{pos}, langerin^{neg}. We found that both LC and DDC supported productive infection with KSHV. Strikingly, while the level of viral DNA replication increased only 4-fold in infected DDC by 24h, we observed a >1 $\log_{10}$ increase in levels of viral DNA in LC. Anti-DC-SIGN mAB inhibited viral infection of DDC as detected by expression of viral proteins and viral DNA, while blocking of langerin on LC did not interfere with viral entry and replication. Infection with KSHV did not alter cell surface expression of langerin on LC, but downregulated expression of DC-SIGN on DDC, as we previously reported for MoDC. Cytokine production in infected LC and DDC was also altered compared to uninfected cells, with an increase in the levels of IL-8, IL-6, and IL-10 in the infected cells. These results indicate that KSHV can target both LC and DDC for productive infection and alter their function, supporting a role for these dermal DC in KSHV infection and pathogen.

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