

Plasmacytoid DCs and anti-HSV CTLs with

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Why is the migration of dendritic cells to lymph nodes important for the immune response?

Hiroyuki Yoneyama: Dendritic cells (DCs) are bone marrow-derived professional antigen-presenting cells (APCs). The function of DCs depends on their maturation stages: progenitors in the bone marrow, precursors in the blood, immature DCs in peripheral tissues, antigen-transporting DCs in the afferent lymphatics, and mature APCs in lymph nodes (LNs) (1). In a steady-state lifecycle, a small number of DCs continually scan self-components at peripheral tissues and maintain peripheral tolerance to self after migrating to LNs. When exposed to danger signals, accelerated traffic of DCs occurs and these newly appeared DCs strongly promote cell-mediated immunity in LNs (2,3). This pathway has been demonstrated only by myeloid DCs (mDCs). We have recently dem-

onstrated that plasmacytoid DCs (pDCs), in contrast, directly enter the LNs from the circulation through activated high endothelial venules (HEVs) (4). Although the route of LN entry is distinct between mDCs and pDCs, each route impacts on DC function. Afferent lymphatic pathway licenses mDCs to act as APCs, while pDCs are primed by interacting with activated HEVs. DCs flexibly determine the type of immune responses in the LNs by summing up the information that they achieve from tissue-environments as well as exogenous factors. Conceptually, LNs are “effector sites” while peripheral tissues are “induction sites” for DCs, in contrast to lymphocytes that encounter antigens at LNs (“induction sites”) and consequently migrate to peripheral tissues (“effector sites”).

What is the role of plasmacytoid DCs?

Hiroyuki Yoneyama: Herpes simplex virus (HSV) have developed numerous mechanisms to escape from the host’s immune response and invade host tissues by accumulating in the draining LNs extracellularly or within the cytoplasm of mDCs migrating from initial target tissues. Infected mDCs have impaired surface MHC class I expression, reduced T-cell stimulatory capacity, and lower cytokine production, and even become virus-producing cells. This is a serious problem for hosts leading

to exacerbation or persistent infections. To overcome this viral immune escape, the host might have evolved a strategy in which pDCs rapidly migrate to systemic LNs via HEVs and help APC function of mDCs by multiple mechanisms (Figure) (4,5). We consider that pDCs play a pivotal role in skewing the DC network from impairment toward activation in HSV-infected LNs. pDC function could be a vital part of the host’s armoury in combating viral evolution.

How can pDCs influence the generation of antiviral cytotoxic T lymphocytes?

Hiroyuki Yoneyama: Although pDCs function poorly as APCs for naïve T cells in a cutaneous

HSV-1 infection model, pDCs produce large amounts of IFN- α , which prevents viral replication,

stimulates NK cells and promotes cross-priming of cytotoxic T lymphocytes (CTLs). In addition, activated pDCs facilitate mDC/APC-T cell interaction in T cell-zones of LNs. When mDC/APC networks are not fully activated to mount anti-HSV CTL immunity, LN-recruited pDCs contact “HSV-impaired” mDCs through CD2-CD2L interaction and provide CD40L-CD40 signaling to impaired DCs. This con-

verts mDC/APC networks from “impaired” toward “recovered” conditions (5). Recovered mDC/APC networks now promote effective CTL cell immunity. pDC-derived chemokines such as CXCL10 further recruit DCs as well as T cells, and cytokines such as IFN- α also accelerate CTL generation. We propose pDCs as “helper DCs” or “immune-networking” DCs rather than “APCs” in anti-HSV immunity.

What kind of model do you use to study this phenomenon?

Hiroyuki Yoneyama: Our study provides a novel concept into antiviral host defense. In response to danger signals, two subsets of DC precursors appeared in the circulation. mDC precursors rapidly migrate into local inflamed tissues to mount antigens (Ags) and later mobilize to the draining LNs to induce T cell immunity (**mDC-mediated linkage of innate and acquired immunity**) (2,3). pDC precursors at the same time migrate

into systemic LNs through HEVs to operate host DC system. This trans-HEV migration is transient depending on activation status of LN HEVs, but activate pDCs to acquire “helper” function (4,5). LN-recruited pDCs produce IFN- α in response to virus Ags and help mDCs/APCs to induce antiviral CTLs (**pDC-mediated helper function**). Concerted recruitment of mDCs and pDCs enables the host to overcome viral escape.

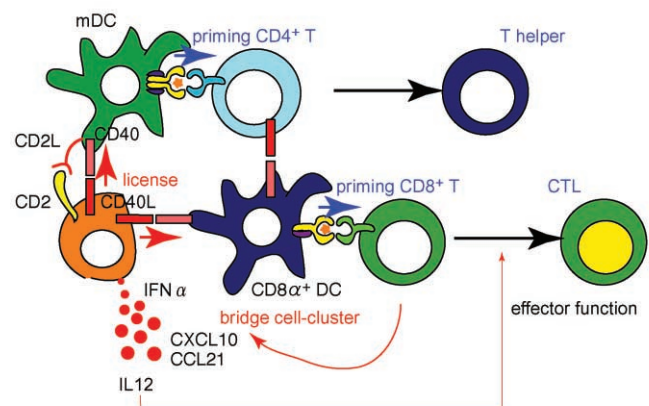


Figure: Helper function of LN-recruited pDCs in the generation of anti-HSV CTLs:

- (1) combined licensing of mDC & CD8 α DC (APC) via CD2/CD40L
- (2) bridging cell-communication of DC/APC-T cell networks via cytokines/chemokines

Can your findings help scientists to develop new therapeutic strategies?

Hiroyuki Yoneyama: Viral escape still creates a major problem in immunotherapy. DC dysfunction is also seen in cancer patients and is a major factor impairing the generation of CTLs. Our study suggests the potent ability of pDCs to improve the activity and communication of impaired DC networks and may provide a novel strategy for the development of

DC-based vaccination, to improve CTL induction against persistent viral infection, such as hepatitis and AIDS, and also in cancer.

REFERENCES

- 1.Yoneyama et al. Int J Hematol 81, 204, 2005
- 2.Yoneyama et al. J Exp Med 193, 35, 2001
- 3.Yoneyama et al. J Exp Med 195, 1257, 2002
- 4.Yoneyama et al. Int Immunol 16, 915, 2004
- 5.Yoneyama et al. J Exp Med 202, 425, 2005