Plasmacytoid dendritic cells in lymphoid organs: comparative studies at the interface between innate and adaptive immunity against HIV

Institut Cochin

Immunology Department

A Hosmalin, G Hoeffel, C Marañon, AC Ripoche
Institut Cochin, Paris

anRS

Dendritic cell Workgroup

J-C Gluckmann, S Boudaly, F Sanchez, M Robledo-Sarmiento
Hôpital St Louis, Paris

B Verrier
CNRS/Biomérieux, Lyon
MVA
ALVAC
Ad5

F Tangy
Institut Pasteur Paris
Measles virus

N Winter, V Abadie Institut Pasteur Paris
BCG

1 **Vaccine vectors are not armed equally to induce immunogenicity**

2 **Plasmacytoid dendritic cells in lymphoid organs: comparative studies**

Vaccine vectors are not armed equally to induce immunogenicity :

Optimizing the interactions of HIV-1 Gag vaccine vectors with human DC

1. **Different vectors used in clinical assays, low *in vivo* immunogenicity and disappointing results of STEP trial**
2. **Murine viral infection models: Innate immune responses following infection influence the following adative immune responses and the prognosis of infection: type I IFN, IL-12, IL10… *Dalod Biron J Exp Med 03***
3. **DC required for naive T cell stimulation**
4. **Each vaccine vector has different effects on DC: correlation with antigenicity and immunogenicity?**

Vaccine vectors are not armed equally to induce immunogenicity :

Optimizing the interactions of HIV-1 Gag vaccine vectors with human DC

All 4 vectors induced Gag expression and were antigenic (induce HIV-specific CD8+ T cell responses)

Only BCG induced complete maturation of MDDC, high production of IL-12p70, and CCR7 expression necessary for naive T cell activation

TLR agonists can be combined to the vectors to restore IL-12p70 production and CCR7 expression

Perspective

Identify TLR agonists that can be used clinically for each DC population

In vivo tests in macaques

Hoeffel et al., in preparation

Plasmacytoid dendritic cells in lymphoid organs: comparative studies at the interface between innate and adaptive immunity against HIV

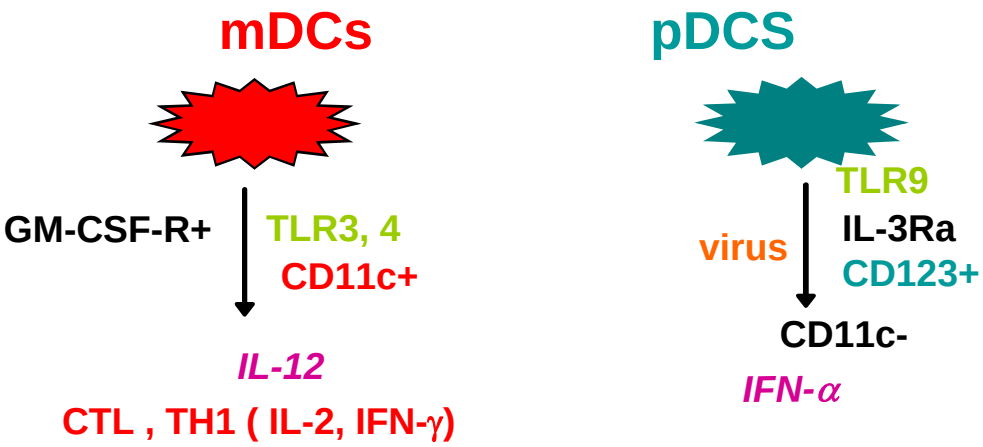
Leila Perié, Michelina Nascimbeni, Stéphanie Louis, Rémi Cheynier, Bruno Vaslin, Roger Le Grand, Michaela Müller-Trutwin and Anne Hosmalin

Immunology Department

1 **Vaccine vectors are not armed equally to induce immunogenicity**

2 **Plasmacytoid dendritic cells in lymphoid organs: comparative studies**

Pathogenesis of HIV infection *in vivo* : Reduced circulating DC counts, Reduced type I IFN and IL-12 production



Reduced numbers of mDC and pDC

Correlation between high pDC numbers, normal *in vitro* type IFN production and viral load control,

absence of immunodeficiency (Kaposi, AIDS)

anRS Agence nationale de recherches sur le sida et les hépatites virales

Institut Cochin

Chronic *Grassi AIDS 1999*

Primary *Pacanowski Blood 20(*

Prediction?

Pacanowski J Inf Dis 2004 Lichtner 2008

Low IFN *Kamga J Inf Dis 2005*

Servet 2002 Müller-Trutwin J Leuko Bio2006

***OTHER TEAM* S: Chronic**

Jones, Donaghy, Stebbing, Imami, Gotch,

Patterson, Knight

Chehimi, Montaner, Trinchieri

Levy, Soumelis, Liu

Rinaldo, Wilson

Anthony

Prieto

Feldman, Siegal, Fitzgerald-Bocarsly

Primary *Levy*

Dendritic cell number defect during HIV infection: Origin?

Central

- **Proliferation**
- **Differentiation**
- **Maturation**

Peripheral

- **Destruction, apoptosis?**
- **Growth factor deficiency?**
- **Homing to lymphoid organs?**

Zou 1997
Foussat 2001
Loré 2001
Zimmer 2002
Choi 2003

Do DC home to secondary lymphoid organs during HIV and SIV infections ?

- Apparent homing of pDC, not cDC, into some spleens from HIV+ patients with late, severe disease, correlates with local proviral load

- Homing of pDC, not cDC, into the lymph nodes of cynomolgus macaques throughout pathogenic SIV infection, including early and chronic stages, starting at the peak of viral load

- Discrete homing of pDC, not cDC, into the lymph nodes of african green monkeys during acute SIV agm infection, at the time of viral load and around day 26,
  followed by a drop in circulating DC counts,
  then by circulating DC rebound
  and normalization

→Therefore the depletion of circulating pDC may be at least partly related to homing into the lymphoid organs, whereas the depletion of circulating cDC seems to be related to different mechanisms
→And depletion of circulating pDC may be related to pathogenesis, as also suggested by correlation studies during HIV infection

M. Nascimbeni, L Perié … Hosmalin in revision
Malleret, Vaslin, Le Grand et al Blood 2008
Diop, Müller-Trutwin, Barré-Sinoussi et al J Virol 2008

What is the role of type I IFN production during HIV and SIV infections ?

- In the two models of SIV infection, a strong viral load peak appears at day 10 post-infection (later if lower dose in cynomolgus); this peak is rarely seen in patients

- Concomitantly, a strong type I IFN peak appears in the plasma, then disappears

- The capacity to secrete type I IFN in vitro after HSV or CpG stimulation is strongly impaired during primary infection in cynomolgus macaques, as during primary HIV infection; conversely, this capacity, which was low before infection, is enhanced in african green monkeys.

→Therefore early production of type I IFN may be important against pathogenicity of HIV/SIV infection

Malleret, Vaslin, Le Grand et al Blood 2008
Diop, Müller-Trutwin, Barré-Sinoussi et al J Virol 2008

Role of dendritic cells during primary infection by VIH et SIV