

POST DOCTORAL POSITION (2 years)

Role of plasmacytoid dendritic cells in Hepatitis C virus immune evasion

Hepatitis C virus infects hepatocytes and is a leading cause of chronic liver disease. Chronicity is believed to result from inability to mount an HCV-specific CD8 cytotoxic T cell response to clear virus-infected cells. The liver is an immuno-privileged organ known to contribute to T cell tolerance to dietary antigens. We recently documented that the liver is enriched in a subset of dendritic cells, called plasmacytoid dendritic cells (pDC), which induce oral tolerance by causing anergy/deletion of CD8⁺ T cells.

The aim of the project is to investigate the role played by pDC located in the liver in immune T cell tolerance to HCV antigens in mice. This will be carried out using mice with liver targeted expression of HCV antigens and by developing a model of tolerance using lipoproteins containing HCV antigens. In these models, we will determine whether i) HCV-specific T cell tolerance could be abrogated by selective depletion of pDC and ii) whether HCV-specific tolerance could be transferred by liver pDC .

Laboratory :

Our laboratory (Team of Dominique Kaiserlian) is located within the INSERM Unit 851, Lyon Gerland and has access to several technical platforms and core facilities of the IFR128 (<http://www.ifr128.prd.fr/ifr128.htm>)

Qualifications

The candidate must have a PhD in the field of immunology with a solid experience in mouse models, analysis of T cell responses and flow cytometry. Basic knowledge and practice in molecular biology and biochemistry will be appreciated. Strong motivation, autonomy and ability to carry out collaborative work with other teams on site are essential.

Salary:

2000-2200 € net/month, for 2 years (CDD INSERM) from a grant from the FINOVI foundation. The post doc position will start in mai 2010.

Application :

Applications should be sent before end of February, by E-mail to postdoc.u851@gmail.com, including :

- - complete CV with list of publications
- - letter of motivation
- - name and E-mail of 2 referees

Interviews of selected candidates will be planned in march 2010.

Hepatitis C virus (HCV) establishes chronic infection by immune escape mechanisms that remains to be understood. Studies from human chronically infected with HCV indicate that immune evasion and inability to clear the infection is associated with impaired differentiation of HCV-specific T cells into IFN γ -producing and cytolytic effectors. Although, evidence for abnormality of circulating antigen-presenting dendritic cells (DC) including plasmacytoid DC (potent producers of Type I IFN) in chronic HCV infection is disputed, little is known on the role of liver DC in protection against HCV. Our working hypothesis is that the liver microenvironment might play a decisive role in the conditioning of DC subsets, that might be exploited by HCV to impair induction of protective T cell-mediated immunity. In this respect, the liver is known as an immunoprivileged organs that contributes to transplantation tolerance and oral tolerance to food antigens. We recently documented that pDC in the liver are greatly enriched (as compared to lymphoid organs), have tolerogenic properties especially on CD8⁺ T cell responses *in vivo* and are essential during the early phase of oral tolerance to dietary antigens. Liver pDC rapidly induce the anergy/deletion of specific CD8 T cells specific for food antigens, resulting in impaired differentiation into IFN γ -producing cytolytic effectors. Moreover, *in vivo* depletion of pDC by injection of specific antibodies prevents oral tolerance and restores *in vivo* priming of functional CD8⁺ effector T cell response. Thus, pDC may play an important role in the pathophysiology of HCV infection, on one hand by silencing HCV-specific T cells in the liver and on the other hand by controlling HCV replication via the production of Type I IFN. In this project, we propose to investigate whether lack of pDC could allow for *in vivo* priming and differentiation of HCV-specific IFN γ -producing cytotoxic CD8⁺ T cells and also examine whether pDC could exert a positive or negative impact on HCV replication in the liver. To this end, we will develop two experimental models. Firstly, to examine whether lack of pDC allows for *in vivo* priming of specific CD8⁺ T cells and differentiation into cytolytic effectors, we will use i) transgenic mice with inducible expression of HCV genome in the liver and ii) normal mice injected with lipoprotein containing the HCV E1 and E2 envelope proteins to target HCV antigens to the liver. pDC depletion will be induced by *in vivo* treatment with a pDC (BST2-Ag) specific mAb or by utilization of SIGLEC-H DTR mice (expressing the Diphtheria toxin under control of the SIGLEC-H promoter) allowing for conditionnal

ablation of pDC. Secondly, we will use and adapt liver-humanized mice transplanted with human hepatocytes and engrafted with human hepatocytes, to examine whether transfer of human pDC (with or without *in vivo* activation by injection of ligands for Toll-like receptor 7 and 9 to stimulate Type I IFN production) reduces or exacerbates HCV replication and liver inflammation *in vivo*. We believe that these *in vivo* studies will allow to determine to what extent pDC could contribute to protection or to immune escape against HCV and this may open up new avenues for therapeutic intervention.