PD Dr Pierre-Yves Mantel – Département OMI (Oncology, Microbiology and Immunology)

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Titre et résumé de la thèse – Title and abstract of the thesis

A Story of Host and Parasite Cohabitation

Immune regulation is a crucial mechanism to maintain homeostasis and host integrity. When the immune system is out of control, reacting against innocuous antigens or overacting against a pathogen, the damages can lead to permanent disabilities or even death. Several mechanisms exist to protect the host against immune pathology and control the immune response. The iTregs, characterized by the expression of the transcription factor Foxp3 play a key role in the maintenance of immune tolerance. We investigated how Foxp3 expression is controlled by analyzing its promoter. The promoter is highly conserved between human, mouse and rat and contains several transcription factor-binding sites that are activated upon activation of the T Cell Receptor (TCR). Strikingly we found that Th2 and Th17 cytokines were inhibiting Foxp3 expression by inducing the GATA3 and RORγt expression. Gata-3 was directly binding to the Foxp3 promoter preventing its expression during a Th2 immune response. Therefore, differentiation into Th2 or Th17 restricts the differentiation into Tregs. Ensuring that in an infectious environment, T cells differentiate into anti-pathogens effector T cells instead of immune suppressive Tregs. Our discovery that Il-4 inhibits Treg induction suggested that during allergies by neutralizing IL-4 with antibodies for examples we might favor the development of the iTreg response.

Pathogens release factors that activate or suppress the immune system. We found that Plasmodium falciparum the causative agent of malaria secretes small vesicles of varying size with potent immune modulatory properties and a role in intercellular communication. In fact, besides activating the immune system the EVs work as small messengers carrying functional cargoes that are transferred to recipient cells. We and other found that EVs are involved in active cell-cell communication to promote transmission to uninfected individuals. In fact, Pf uses the release of EVs as a social mechanism of sensing a hostile host environment and triggering sexual differentiation. To gain insights into the mechanisms of cellular communication, we characterized EV content and found the EVs contain cargoes from both human and parasite origin. When released EVs have a very potent effect on the vascular function. Therefore, EVs may contribute to the pathology observed in cerebral malaria and the regulation of the immune response.

Therefore, our research is focused on the identification of novel mechanisms of parasite-host interactions during malaria. Our projects have the potential to develop new therapies and novel diagnostics.

Titre et résumé de la leçon d'essai – Title and abstract of the inaugural lecture

Comment le parasite meurtrier de la malaria manipule notre système immunitaire

D'après l'OMS, environ 200 millions de personnes sont infectés par le paludisme chaque année dans le monde. La maladie va causer la mort d'environ 500'000 personnes en particulier des enfants dans les régions d'Afrique subsaharienne.

Le paludisme est causé par les parasites du genre Plasmodium, qui sont transmis par la piqûre d'un moustique. Le parasite va ensuite durant un processus de différentiation complexe et hautement régulé, après avoir traversé le foie, atteindre la circulation sanguine. Les symptômes cliniques se manifestent durant la phase sanguine, durant laquelle le parasite se multiplie massivement à l'intérieur de globules rouges.

Durant l’évolution, le parasite a développé de nombreuses stratégies afin d’éviter l’élimination par le système immunitaire. En effet, le parasite est devenu un expert pour moduler la réponse immunitaire.
Durant cette leçon, nous allons discuter des éléments de bases du cycle de vie du parasite et dans une deuxième partie, nous parlerons des mécanismes de régulation immunitaire qui permettent aux parasites de survivre dans un élément hostile.