ED BIO SORBONNE PARIS CITE

Renseignements relatifs à l'Unité de Recherche :

Label et intitulé : UMR_S1134, Inserm/ Institut National de la Transfusion Sanguine/Université de Paris, Biologie Intégrée du Globule Rouge

Nom et prénom du Directeur : Yves Colin Aronovicz

Téléphone : 01 44 49 30 93 Télécopie : 01 43 06 50 19

Courriel: yves.colin-aronovicz@inserm.fr

Renseignements relatifs à l'Equipe :

Nom de l'Equipe d'Accueil : Physiologie du Globules Rouge Normal et Pathologique

Nom et prénom du responsable : Caroline Le Van Kim

Qualité du responsable : Professeur Université de Paris

Téléphone : 01 44 49 30 46 Télécopie : 01 43 06 50 19

Courriel : caroline.le-van-kim@inserm.fr

Renseignements relatifs au sujet de thèse :

Nom et prénom du Directeur de thèse (HDR) : Yves Colin Aronovicz

Qualité : Directeur de Recherche (DR1) CNRS

Téléphone : 01 44 49 30 93 Télécopie : 01 43 06 50 19

Courriel : yves.colin-aronovicz@inserm.fr

Involvement of the myeloid lineage in SCD pathophysiology

State of the art

Sickle cell disease (SCD) is a life-threatening hemoglobinopathy caused by a unique genetic mutation in the β-globin gene. SCD is associated with acute and chronic complications, including frequent painful vaso-occlusive crisis (VOC) that require hospitalization. VOC is not only due to the occlusion of microvessels by the sickled red blood cells, but also result from vascular inflammatory mechanisms that involve pancellular activation, recruitment and adhesion of neutrophis, platelets and red cells to the endothelium of blood vessels.

Interactions between circulating **neutrophils** and other blood cells as well as with the vascular endothelium are thought to initiate the VOC process, but the specific triggers in its initiation and propagation are not well understood. In patients, VOC are often prompted by infections (viral or bacterial), hemolysis, changes in temperature, physical exertion or other epigenetic factors. In mice models of SCD, VOC-like processes can be triggered by a potent inflammatory stimulus (TNF cytokine or lipopolysaccharide [LPS] administration) and hypoxia-reperfusion. But the pathway by which these different triggers can lead to the vaso-occlusion

cascade (s) is still unknown. The consequence is the lack of specific treatment for the crisis, which is still limited today to the use of analgesics, until the process overcomes of its own.

Beyond the acute painful complications, the severity of SCD is due to the progressive dysfunction of many organs including kidney, heart and lung. Chronic inflammation is partly responsible for this morbidity, since patients exhibit constant **high leucocyte counts**, the reason why is still unknown. This high leucocyte count at steady state is statistically correlated with the severity of the disease and the early mortality of the patient. We hypothesized that the origin of this basal high leucocyte count could be due to abnormal myeloid differentiation in inflammatory context, and/or to a defect in the elimination of abnormal (activated and aged) circulating neutrophils.

PhD Project:

I. Role of neutrophils in different models of vaso-occlusive processes

- ➔ Characterize whether different VOC stimuli (infectious, inflammatory, hypoxic, hemolytic) provoke similar or distinct mechanisms of cellular and inflammatory interactions in the vasculature, in dynamic flow adhesion experiment with whole blood from SCD patients on cultivated endothelial cells.
- ➔ Analysis of the effect of each stimulus on neutrophil activation (characterization of surface markers of activation by flow cytometry, protein quantification with western blot)
- ➔ Analysis of the effect of each stimulus on neutrophil interaction with other blood cells (platelets/neutrophils aggregates, red cells/neutrophils aggregates)

II. Decipher the origin of high neutrophils count in SCD

- ➔ Analysis of myeloid progenitors/precursors in peripheral blood from SCD patients using specific surface markers (CD34, CD38, CD90, IL-3R, CXCR4, CXCR2, CD11a, CD11b, CD15, CD16).
- ➔ Transcriptomic analysis of the myeloid progenitors from SCD patients in order to identify the activated cytokine pathway.
- ➔ In vitro myeloid differentiation (granulopoiesis) from CD34+ progenitor cells of SCD patients.

The PhD student will work on hematopoiesis in sickle cell disease (basic science) as well as the role of leukocytes in the vaso-occlusive crisis (translational medicine). A background in cell culture and flow cytometry is required and experience in stem cell biology would be appreciated. The PhD student will use the microfluidic platform of the unit for functional adhesion studies of blood cells.