A brain-to-skin axis orchestrating tissue-resident macrophages healing properties

Dr. Guillaume Hoeffel

CIML, Marseille, France

The skin represents both the frontline of defense against external threats, and the largest sensory organ of touch. The somatosensory nervous system has become central to understand skin homeostasis. We recently described a new mechanism by which a subset of sensory neurons (GINIP+) sustained dermal-resident Tim4+ macrophages (DRM) healing properties upon skin injuries (Hoeffel et al., Nature 2021). More recently, we also observed the involvement of the hypothalamus-pituitary- adrenal (HPA) axis in orchestrating myeloid cell healing responses, suggesting an integral brain-to-skin axis constantly tuning its integrity.

Confocal microscopy revealed that embryonically-derived Tim4+ DRM were embedded in a neurovascular niche controlling neutrophil infiltration upon skin injury. We then detected an acute release of endogenous Glucocorticoids (GCs) in the bloodstream, suggesting the involvement of the central stress pathway. To unravel the neuronal circuits relaying skin lesions to the brain, we mapped the activated areas using c-Fos staining, revealing the paraventricular nucleus to initiate the HPA cascade. We then monitored key regulatory functions of GCs on myeloid cells during the skin healing process through high dimensional spectral flow cytometry analysis in different tissues.

First, GCs promoted the expansion of myeloid precursors directly in the bone marrow. Second, fate mapping and conditional deletion of the GC receptor (encoded by Nr3c1) in monocytes revealed the regulatory action of GCs on efferocytosis functions of monocyte-derived macrophages infiltrating the skin lesion.

Deciphering the nature of peripheral and central neuronal circuits promoting tissue integrity and repair will provide new leads for regenerative medicine strategies.