**Macrophages at Work or the Secret of Indelible Tattoos**

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While, studying specific sentinel cells of our immune system residing in the skin, we figured out how those specific sentinel cells of our immune system were involved in tattoo persistence.

Immune cells lining our skin are very complex. Among those cells we can find macrophages. Due to their capacity to phagocyte cellular debris, invading organisms, and dying cells, macrophages contribute to tissue homeostasis and immune protection.

For many years, it has been very difficult to decipher, within tissue parenchyma including the skin, macrophages from other myeloid cells of the immune system such as dendritic cells. In a previous study, we could define markers that were very specific for macrophages. One marker was chosen to construct a novel and innovative mouse model that would allow us to deplete macrophages *in vivo* and therefore to study in depth their immunobiology *in vivo*.

While we were studying this model we discovered a type of macrophages that was previously described in human dermis but its equivalent in mouse dermis was yet unknown. Indeed, we found that the skin of black mice contains macrophages that have ingested melanin that is released by dying melanocytes and that were named melanophages.

Melanin can be regarded as our skin natural pigment and while we were analyzing the dynamics and turnover of melanophages, we started wondering how the pigments that are contained in tattoo ink were retained inside the skin. In embarking in such project we were quite surprised to see that only very limited knowledge was available on tattoo persistence and on the skin cells that uptake the ink.

Driven by curiosity, we decided to open a tattoo shop in our mouse facility and eventhough we are not yet the best tattoo artists in the world, we succeeded tattooing green stripes on mouse tails. First, we showed that for macrophages, tattoo ink plunged deep in the skin is considered as foreign material, potentially harmful and therefore, it is their duty and their mission to try their best to discard it. Indeed, we showed that macrophages engulf the invading ink much as they would a pathogen. Unfortunately for the macrophages, and fortunately for the tattooed fellow, they fail to degrade the ink, so they sit in place for good, their one-celled bellies distended with pigment.

Using our novel and innovative mouse model, we showed that depletion of macrophages few weeks after tattooing succeeded to deplete ink-laden macrophages whereas the green stripes on the mouse tails were unchanged. Indeed, we found that macrophages derived from bone-marrow derived monocytes were restored within few days post depletion and were able to phagocytose the ink released by the dying macrophages. Our results questionned previous human studies suggesting that tattoo pigment was contained in long-lived low proliferative dermal macrophages and therefore that tattoos might endure simply because cell turnover is very slow. Instead, our study suggested that tattoo persistence could be explained by dynamic cycles of pigment release and recapture.

Our finding may allow to propose new strategies for tattoo removal procedures. Professional tattoos last for years or decades and when no longer desired, they can be removed through the use of quality-switched lasers. Laser pulses lead to cellular lysis, fragmentation of the tattoo pigments and their lymphatic transportation.  Several cycles of laser treatment are required to achieve tattoo removal and some tattoos remain immune to full removal. These difficulties are generally accounted for by the fact that a fraction of the fragmented pigment particles remained at the tattooed site and are recaptured by neighbouring macrophages, a possibility formally demonstrated in our study. Considering the long duration needed for the reconstitution of the pool of dermal macrophages and the recapture of the whole released pigments, tattoo removal can be likely improved by combining laser surgery with the transient ablation of the macrophages present in the tattoo area. Accordingly, the fragmented pigment particles generated using laser pulses will not have the possibility to be immediately recaptured by dermal macrophages, a condition increasing the probability of having them drained away via the lymphatic vessels.

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