The fate and plasticity of inflammatory macrophages during peritonitis

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Introduction
Acute peritonitis leads to transient disappearance of resident peritoneal macrophages and recruitment of large numbers of transcriptionally distinct inflammatory monocyte-derived macrophages. The fate of these inflammatory macrophages after resolution of inflammation remains controversial. Some studies suggest the majority die out while others indicate they convert into resident macrophages. Using a novel adoptive transfer system we investigated the long-term fate of inflammatory macrophages.

Materials & Methods
PKH26-PCL dye was used to distinguish resident macrophages from inflammatory macrophages during the acute phase of zymosan induced peritonitis. The fate of these cells was determined following adoptive transfer into naïve or inflamed cavities of congenic Ly5.1+ mice. Alternatively, these populations were transferred into a cavity depleted of endogenous macrophages to ascertain to what extent the microenvironment dictated their fate.

Results
Transfer into a mirroring inflamed environment indicated that inflammatory macrophages present at peak inflammation persisted and underwent phenotypic conversion to a resident phenotype following resolution but remained transcriptionally distinct from bona fide resident macrophages. We identified markers that distinguished resident and converted inflammatory macrophages for months after inflammation resolution. These converted inflammatory macrophages produced less inflammatory cytokines in response to in vitro stimulation with LPS than bona fide resident macrophages. In the absence of endogenous resident macrophages, inflammatory macrophages where able to acquire a transcriptome more similar to resident macrophages, providing evidence of their potential to convert.

Conclusion
These data indicate that inflammatory macrophages recruited during peak inflammation persist following inflammation but remain transcriptionally and functionally distinct. In the absence of endogenous macrophages inflammatory macrophages acquire a more resident like transcriptome suggesting presence of incumbent resident cells inhibits this conversion. Thus, our data support a model whereby niche competition is a temporal determinant of macrophage identity post inflammation. Hence, inflammation leads to a long-term altered homeostasis in the origin and function of the peritoneal macrophage compartment, with a population predominantly seeded during embryogenesis being partially replaced by macrophages differentiated under inflammatory conditions.

Keywords : peritonitis, macrophage, inflammation, resolution
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