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Letters

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The Origin of Tissue-Resident Macrophages: When an Erythro-myeloid Progenitor Is an Erythro-myeloid Progenitor

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Sheng, Ruedl, and Karjalainen published in *Immunity* (Sheng et al., 2015) a fate-mapping model where the expression of Cre recombinase was inducible in *Kit*-expressing cells (*Kit*-MeriCreMer mice). In this system, the authors also revisited the origin of adult tissue-resident macrophages. For a long time, these macrophages have been assumed to be monocyte derivatives and hence ultimately to originate from adult bone marrow stem cells. In recent years, this view has been completely revised by the work of several groups (Schulz et al., 2012; Hashimoto et al., 2013), and in the field there is now a view that resident macrophages in most tissues do not arise from adult hematopoietic stem cells (HSCs) but rather develop at pre-natal stages and persist autonomously in adult tissues (at least under steady-state conditions). However, the precise cell of origin for tissue-resident macrophages during embryonic life (stages up to approximately day 10 of prenatal development) or fetal life (stages from approximately day 10 of prenatal development to birth) has been unknown until recently.

On the basis of fate mapping using several independent inducible and constitutive mouse models, we recently tracked the stage of origin of tissue-resident macrophages to times prior to embryonic day 10.5 (E10.5) in development and reported the identification of yolk-sac-derived erythro-myeloid progenitors (EMPs) as the main source of fetal and adult tissue-resident macrophages (Gomez Perdiguero et al., 2015). A subsequent report confirmed our findings that yolk-sac-derived EMPs are the origin of tissue macrophages and further suggested that macrophages arise either directly from EMPs or later from fetal monocytes that are, however, also derived from EMPs (Hoeffel et al., 2015).

Sheng et al. (2015) now challenge these two reports by claiming that tissue-resident macrophages do not originate from yolk-sac-derived EMPs but, instead, arise from HSCs that develop independently from the yolk sac in the embryo or its fetal liver. They base their claim essentially on two findings. The first is that in their *Kit*-driven fate-mapping system, they failed to label tissue-resident macrophages (with the exception of microglia) when they injected tamoxifen on E7.5. In contrast, using *Tie2*-driven fate mapping, we found the highest frequencies of fate-mapped cells when we injected tamoxifen on this very same day (E7.5) (Gomez Perdiguero et al., 2015). This difference simply reflects the fact that *Tie2* labels hemogenic endothelial cells, whereas *Kit*$^+$ EMPs appear at E8.25 (McGrath et al., 2015). Consequently, E7.5 yolk sac cells, including those that give rise to tissue-resident macrophages, can be genetically marked by *Tie2*-MerCreMer but not by *Kit*-MeriCreMer, which is exactly what Sheng, Ruedl, and Karjalainen found. The second argument Sheng, Ruedl, and Karjalainen put forward to back up their claim that yolk-sac-derived EMPs are not the progenitors of tissue-resident macrophages is a flow cytometric analysis of cells included in their *Kit*-driven fate mapping. In mice receiving tamoxifen on E7.5, they detected (in analysis on E10.5) in the yolk sac marked cells that they thought were EMPs. Their argument developed to say that if EMPs but not tissue-resident macrophages are labeled on E7.5, then this dissociation shows that EMPs cannot be the progenitors of tissue-resident macrophages. We could subscribe to this conclusion if the cells analyzed by Sheng et al. indeed qualified as EMPs. However, these cells fall short of satisfying many well-established EMP criteria. First, EMPs are characterized by expression of KIT, CD41, CD93 (AA4.1), CD16/32, and CD45 and do not express SCA1 (McGrath et al., 2015). Of note, the cells that Sheng et al. consider to be EMPs have a different phenotype and hence cannot be the same cells. Second, in addition to showing cell-surface phenotype, it is essential to demonstrate that the cells under investigation have the expected function, i.e., the potential to give rise to both myeloid and erythoid progeny. In our report, we had included in-depth in vivo and in vitro functional analyses, including progenitor frequencies for myeloid (M), granulocytic (G), erythoid (E), and megakaryocytic (Mk) colonies, as well as mixed G-M and E-Mk colonies (Gomez Perdiguero et al., 2015). In brief, both phenotypically and functionally we had unequivocally identified the cells as EMPs. Unfortunately, the study by Sheng et al. (2015) failed by the same criteria to demonstrate that the cells that they labeled on E7.5 were in fact EMPs. Sheng, Ruedl, and Karjalainen state strongly in the title and summary that, with the exception of microglia and, partially, epidermal Langerhans cells, most tissue-resident macrophages are descendants of classical fetal HSCs rather than EMPs. For the reasons

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outlined above, we believe that their published data do not support this claim.

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