to progress into an epithelioid phenotype and the terminology “epithelioid macrophage” has been regarded as misleading. We disagree with these comments.

First, we did not invent “epithelioid macrophages,” but carefully assigned platelet-transformed macrophages as epithelioid-like cells based on their transcriptional/genetic hallmarks and their cellular morphology. Second, the fact that macrophages develop into epithelioid phenotypes is well documented in granulomatous diseases and particularly in tuberculosis [2, 3]. Multiple lines of evidence, including various animal models, indicate that macrophages with epithelioid appearance (high cytoplasm/nucleus ratios and diffusely eosinophilic cytoplasm [4, 5]) are induced during tuberculosis/bacille Calmette-Guérin (BCG) infection [6, 7] or stimulation with mycobacterial lipids [8]. Such epithelioid macrophages have been described in mice infected with BCG [7] and Mycobacterium tuberculosis [9, 10]. They are recruited into tissue upon stimulation with BCG-coated/mycobacterial lipid-coated beads or mycobacterial glycolipids [8, 11]. More recently, epithelioid macrophages were thoroughly characterized in a nonhuman primate model of tuberculosis. The cells stained positive for macrophage/myeloid cell markers (CD11c, CD68) and for HAM56, a foamy cell marker, thereby indicating their origin and occurrence of mixed phenotypes [6]. Epithelioid macrophages contained M. tuberculosis and at the same time expressed secretory abilities (propensity to release nitric oxide based on the immunostaining pattern). The platelet-transformed macrophages in our ex vivo set-up similarly released cytokines and chemokines, thus acting as secretary cells. Notably, our analyses were performed on bulk-transformed human macrophages and, as such, the capacity to internalize bacteria or release mediators could not be fractionated for foamy, giant, or epithelioid-like cells. While acknowledging this technical limitation of our study, we strongly disagree with the assertion of neglecting the existence and myeloid origin of epithelioid macrophages.

In sum, we maintain that epithelioid macrophages are phenotypes with distinct ontogeny and are endowed with several functions relevant for tuberculosis outcome. Additional new roles of such transformed macrophages remain to be uncovered by future studies.

Our investigations did not aim at the development of diagnostic tests or vaccines, but rather at identifying roles of platelets in tuberculosis pathogenesis and characterizing transformed macrophages in this disease. Moreover, we do not exclude the presence of cells of lymphoid origin, such as some plasmacytoid dendritic cell subsets in tuberculous granuloma, which may express an epithelioid appearance [12]. In fact, our group recently reported the presence of granzyne B-positive plasmacytoid dendritic cells in lymph node granulomas from tuberculosis patients [13]. Rather, we acknowledge the complexity of cellular types involved in granuloma formation and stability. In this context, macrophages and their transformed subtypes are critical for understanding mechanisms underlying disease progression or protection within granulomas [14].

On behalf of all authors (see [1]), and editorial authors: G. Lugo-Villarino and O. Neyrolles (see [15]).

Notes

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Reply to Crawford

To the Editor—We thank Dr Crawford for his interest in our work. In our article, we report that platelets induce macrophage transformation in cells with foamy and/or heterokaryon phenotypic appearance paralleled by type II macrophage/epithelioid transcriptional signature [1]. These cells interacted with mycobacteria because they phagocytosed bacilli and released primarily regulatory mediators. Although we emphasized the mixed phenotypic features (foamy, giant, multinucleated) and the “epithelioid-like” characteristics of the platelet-transformed macrophages, concerns have been raised by Crawford regarding the propensity of macrophages


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