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Malarial pigment does not induce MMP-2 and TIMP-2 protein release by human monocytes

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Dear editor,

In the recent years growing evidence on the involvement of human matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) in cerebral malaria (CM) has been reported[1] and a role for malarial pigment haemozoin (HZ) has been proposed[2,3]. In a recent work my group showed that in human microvascular endothelial cells HZ induced de novo MMP-9 protein release and activity without affecting basal release of its physiological inhibitor TIMP-1, whereas HZ upregulated TIMP-2, endogenous inhibitor of MMP-2, whose basal production was not altered[4]. On the other side, in human monocytes HZ was exhaustively shown to enhance basal expression, release and activity of MMP-9[5-8].

Here the effects of HZ on MMP-2/TIMP-2 protein release by human adherent monocytes were investigated. After 2-hours HZ phagocytosis, cells were washed and incubated for 24 hours as previously indicated[7]; therefore, cell supernatants were collected and proMMP-2 and TIMP-2 were analyzed by western blotting, whereas levels of active MMP-2 were measured by gelatin zymography, according to previous protocols[4,5]. In each set of experiments (all performed in triplicate) proMMP-2, active MMP-2 and TIMP-2 proteins were not detected in supernatants of unfed monocytes, and HZ was not able to induce de novo any of those molecules.

Notably, these observations fit with a previous work performed by my group, where the early mRNA expression of a complete panel of cytokines and cytokine-related molecules (including MMP-2 and TIMP-2) in human monocytes was analyzed through a macro-array approach: in this work, MMP-2 and TIMP-2 mRNA basal levels were not altered by HZ[9]. Despite being negative evidence, in my opinion these data might be useful in order to better understand the complex pattern of interactions between HZ and MMPs/TIMPs in the context of CM pathogenesis. Additionally, they highlight the importance of a careful differential analysis of the effects of HZ on MMPs/TIMPs according to cell typology. Nevertheless, future post-mortem studies showing the final MMP/TIMP balances as a result of interactions among different specialized cells are strongly encouraged: indeed, at present only one work described enhanced levels of human MMP-1 in brains of patients with CM[10], whereas mean levels of human gelatinases MMP-2 and MMP-9, along with those of their inhibitors TIMP-2 and TIMP-1, remain unknown.

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