

Increased TIMP Levels in Malaria Patients: Risk or Protective Factors?

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Despite the recent decline in estimated malaria cases and deaths - 655,000 deaths among more than 200 million clinical cases worldwide registered in 2010 by World Health Organization (WHO) [1] - malaria remains so far an alarming emergency in developing countries, including Africa and South-East Asia. Thus, it appears urgent to identify new affordable markers for early diagnosis of malaria complications and new targets for primary and adjuvant therapy.

Recently, it has come to light that Tissue Inhibitors of Metalloproteinases (TIMPs) are involved in malaria disease state. These molecules were originally characterized as endogenous Matrix MetalloProteinase (MMP) inhibitors, thus playing a key role in turnover of extracellular matrix and shedding of cell surface molecules [2]. Additionally, TIMPs have important roles in a broad spectrum of MMP-independent biological activities, including cell survival, cell growth and differentiation, cell migration, angiogenesis, and synaptic plasticity [3,4].

Currently, our understanding of TIMPs in malaria manifests from only a few studies showing dysregulated TIMP levels in different *in vitro* and *in vivo* malaria models. In human adherent monocytes cultured *in vitro*, nHZ (a lipid-bound ferriprotoporphyrin IX crystal produced by *Plasmodium* parasites after haemoglobin catabolism) induced inflammation-mediated expression and release of TIMP-1 through p38 MAPK- and NF- κ B-dependent mechanisms [5], without affecting TIMP-2 production [6]. In human microvascular endothelial cells, either *P. falciparum*-IRBCs or nHZ promoted TIMP-2 but not TIMP-1 protein release [7,8]. *In vivo*, CM-sensitive mice infected with *P. berghei* ANKA displayed increased mRNA expression of TIMP-1 in the brain, and both TIMP-1 and -3 mRNA was increased in the liver and spleen, whilst mRNA levels of TIMP-2 and -4 remained unchanged [9]. Increased serum levels of TIMP-1 were also found in Rhesus macaques (*Macaca mulatta*) experimentally infected with *P. coatneyi*, a simian malaria parasite that closely mimics the biological characteristics of *P. falciparum* and replicates the multisystemic dysfunction of human severe malaria [10]. Finally, human patients with severe or uncomplicated malaria displayed higher serum TIMP-1 levels compared to healthy controls, thus suggesting a potential role for TIMP-1 as a diagnostic marker [11].

Still, it is not clear whether higher TIMP levels in malaria patients should be considered protective or risk factors. In this context, the case of TIMP-1 is paradigmatic. One major function of TIMP-1 is to counteract and modulate the numerous effects of MMP-9, which include degradation of the sub-endothelial basal lamina, modulation of the activity of several pro-inflammatory molecules, disruption of tight junctions, and impairment of haemostasis [2], all of which comprise key roles in CM. Thus, it is attractive to hypothesize that increased TIMP-1 levels are a protective factor in malaria prognosis, as they could contrast the potentially detrimental effects of nHZ-enhanced MMP-9 [12]. However, *in vitro* MMP-9/TIMP-1 stoichiometric ratios and total gelatinolytic activity measured in nHZ-fed monocyte supernatants have been shown to be significantly higher than in controls, suggesting that nHZ-dependent induction of TIMP-1 is not sufficient to counterbalance nHZ-enhanced MMP-9 levels, and arguing against TIMP-1 ability to act as a protective factor in this context [5]. What is

more, *in vivo* TIMP-1 serum levels correlated with disease severity in Gabonese children with malaria, suggesting a potential role for TIMP-1 as a risk factor [11].

Intriguingly, TIMP-1 could play a detrimental role through an MMP-independent mechanism. MMP-independent roles for TIMP-1 in biological processes include anti-apoptotic effects of TIMP-1 in several human cells, such as Burkitt's lymphoma, breast epithelial cells, and cardiomyocytes [3,4]. Recently CD63, a member of the tetraspanin family, was identified as a cell-binding partner for TIMP-1 in human mammary epithelial cells, and CD63 down-regulation with shRNA resulted in reduced TIMP-1 binding and restored cell apoptosis [13]. Interestingly, nHZ-fed monocytes do not undergo apoptosis, despite increased inflammation and functional impairment [14,15]. Since CD63 is constitutively expressed by human monocytes [16], it is intriguing to speculate that nHZ-enhanced TIMP-1 levels might prevent apoptosis of functionally impaired nHZ-fed cells through CD63-dependent mechanisms. Additionally, there are several reports describing MMP-independent abilities of TIMP-1 to inhibit cell growth and differentiation [3,4]. These TIMP-1 properties may be crucial for nHZ-fed monocytes, since these cells have been shown not to mature to dendritic cells [17] and not to coordinate erythropoiesis [18].

Future investigation is needed to ascertain whether enhanced TIMP levels may contribute to worsen the clinical course in malaria patients as a consequence of their MMP-independent anti-apoptotic or growth/differentiation-inhibitory properties. Therefore, more extensive research on the functional role of TIMPs in malaria, along with a better understanding of MMP-independent TIMP functions will be welcomed in order to find new tools for differential diagnosis and therapy of severe malaria.

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