Human and Mosquito Lysozomes in Malaria: Old Molecules for New Approaches towards Diagnosis, Therapy and Vector Control

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As a consequence of the global eradication program recently launched by charity foundations [1], World Health Organization (WHO) officially registered in 2010 a decline in estimated malaria cases and deaths, with 655,000 deaths counted among more than 200 million clinical cases worldwide, of which 91% due to Plasmodium falciparum [2]. Nevertheless, malaria remains so far an alarming emergency in developing countries, as the vast majority of cases occur in Africa (81%) and South-East Asia (13%) [2]. Thus, it appears still urgent to identify any parasite or host molecules which might serve as new affordable markers for early diagnosis of malaria complications [3], or as new targets for primary and adjuvant therapy [4] along with vector control [5].

In this context, lysozomes could be good candidate molecules. These enzymes are antibacterial proteins defined by their ability to hydrolyze β-1,4-glycosidic linkage between N-acetylmuramic acid and N-acetylgalcosamine of peptidoglycan in the cell wall of bacteria (muramidase activity) [6]. Three major distinct lysozyme types showing high level of homology have been identified in the animal kingdom: c-type (chicken-type), present in several members of the Chordata, including humans, and different classes of the Arthropoda, including mosquitoes; g-type (goose-type), in few members of the Chordata and in some bivalve molluscs; and i-type (invertebrate-type), in the invertebrates [6]. Human lysozyme was the first mammalian lysozyme to be sequenced and served as a model protein for a wide variety of studies [7]. Interestingly, in the recent years the involvement of both human and mosquito lysozmes in malaria has been observed independently by several research groups.

Natural haemoozin (nHZ, malarial pigment), a lipid-bound ferritropolyporphyrin IX crystal produced by Plasmodium parasites after haemoglobin catabolism, was shown to promote in vitro the early release of human lysozyme from adherent monocytes [8]. Such an effect was mediated by the increased production of three pro-inflammatory molecules (TNFa, IL-1β and MIP-1α/CCL3), and was dependent on activation of p38 mitogen-associated protein kinase (MAPK) and NF-kB pathways [9]. Moreover, 15-hydroxyeccosatetraenoic acid (15-HETE), a major component of the lipid moiety of nHZ, was identified very recently as the molecule responsible for the most part of these effects [10].

Consistently, the plasma levels of lysozyme [11] and the number of nHZ-containing leucocytes in the peripheral blood of P. falciparum-infected patients [12-14] correlated well with parasitaemia degree or disease severity. On the other hand, the mosquito homologue of human lysozyme was shown to bind to oocytes of Plasmodium berghei and falciparum in Anopheles gambiae, stephensi, and dirus, and therefore facilitate their development within the vector [15,16].

These findings suggest that human lysozyme may represent a likely marker for early diagnosis of complicated malaria as well as a putative target for adjuvant therapy, whereas mosquito lysozyme could be addressed as a new target for insecticides to be used in vector control. Although further investigation is certainly required, it is intriguingly to speculate that old well-known enzymes such as lysozymes might reveal themselves as very relevant molecules to be targeted by innovative and cost-effective tools to fight malaria.

References
12. Amodu OK, Adeyemo AA, Olumese PE, Gbadegesin RA (1998) Intraleucocytic leucocyte degranulation in Plasmodium berghei and Plasmodium falciparum, and therefore hematozoa as very relevant molecules to be targeted by innovative and cost-effective tools to fight malaria.
