Sickle Cell MicroRNAs Inhibit the Malaria Parasite

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Detailed Terms
Sickle cell hemoglobin conveys resistance to malaria. In this issue of Cell Host & Microbe, LaMonte et al. (2012) demonstrate a surprising mechanism for this innate immunity. A microRNA enriched in sickle red blood cells is translocated into the parasite, incorporated covalently into P. falciparum mRNAs and inhibits parasite growth.

LaMonte et al. (2012) now add a further layer of complexity to the interactions between the host erythrocyte and the P. falciparum parasite (Figure 1). They find that at least two human microRNAs (miRNAs), miR-451 and miR-233, are more abundant in both sickle cells and in the epidemiologically relevant sickle cell trait cells compared to normal red blood cells. In tightly controlled experiments, they show that miR-451 is translocated into the parasite, where it is incorporated covalently into P. falciparum miRNAs, leading to an inhibition of mRNA translation and a modest but significant reduction in parasite growth. When overexpressed in normal erythrocytes, miR-451 and miR-233 reduced parasite growth; conversely, blocking the erythrocyte to parasite translocation of miR-451 and miR-233, using 2'-O-methyl antisense oligonucleotides, diminished malaria resistance in both sickle cell and sickle cell trait cells.

Why any miRNAs are present in mature erythrocytes is a mystery, since there is no ongoing protein synthesis. Red blood cell miRNAs like miR-451 and miR-233 are generated during erythroblast proliferation and differentiation, prior to enucleation. miR-451 is induced during red blood cell development and is important for formation of erythrocytes (Dore et al., 2008), but it is unclear why it is retained in mature erythrocytes or why its level is higher in sickle than normal red blood cells. Experimentally, miRNAs can be introduced into mature erythrocytes, so exogenous miR-223 or miR-451 could possibly be used therapeutically in treating malaria.

How miRNAs are incorporated into intracellular malaria parasites is also unknown. Plasmodium parasites are contained within a parasitophorous vacuolar membrane, and thus the miRNA would have to cross from the red blood cell cytosol through both this membrane and the parasite’s plasma membrane. Direct visualization of mir-451 in the parasitophorous vacuolar membrane will need to be reconciled with its activity within the parasite. There is a precedent for this, however, as one can use preloaded erythrocytes to introduce plasmid DNA into the parasite (Deitsch et al., 2001), although the efficiency of this process is very low at ~1 in 10^5 cells. It will be of great interest to elucidate the mechanism of miRNA translocation, as this may form the basis for more efficient genetic manipulation of this Plasmodium species.

Plasmodium parasites do not contain Dicer or any Argonaute homologs that comprise the RISC complex. RNA
interference, including conventional functions of miRNAs, is not functional in these organisms. Thus, it was a huge surprise that the translocated miRNAs became covalently linked to certain Plasmodium mRNAs, forming chimeric RNAs. Indeed, several transcripts in a Plasmodium EST database contain miR-451 at their 5’ ends, and this linkage was subsequently confirmed by both real-time PCR and northern blots on parasite material. Covalent linkage requires a trans-splicing event, but in unicellular eukaryotes this has only been observed in kinetoplastid organisms, where a leader sequence is spliced onto the 5’ end of all RNA transcripts during processing and maturation (Sutton and Boothroyd, 1986). In P. falciparum, miRNA tagging occurs to a minority of transcripts, including genes such as PKA-R, PEAMT, and the 28S and 18S rRNAs. We do not know what determines the specific enrichment of certain miRNAs or the incorporation of these miRNAs to specific parasite mRNAs.

This study raises many other questions. Has increased miRNA-451 or miR-223 expression in red blood cells been selected for as a malaria resistance factor, similar to the selection for other red blood cell disorders? Why does a reduction in PKA-R result in reduced parasite proliferation and increased conversion to sexual stage parasites? What, if any, are the functional consequences of the other miRNAs differentially regulated between HbSS and HbAA? Is there conservation of this mechanism in protection against other Plasmodium species? What is the relative contribution of miRNA-based inhibition of parasite growth in HbSS erythrocytes compared to other postulated mechanisms of protection, particularly under low oxygen tension when inhibition of parasite growth is most marked (Pasvol et al., 1978)?

Clearly, Lamonte and colleagues have revealed a startling and unique mechanism of cross species trans-splicing in P. falciparum-infected erythrocytes where the effector molecule of parasitic inhibition is the miRNA itself.

REFERENCES


