The protozoan parasite *Plasmodium* infects a wide range of warm-blooded hosts and causes malaria in humans. These parasites undergo complex developmental changes in both a mosquito vector and host, including asexual and sexual cycles (see figure). Asexual reproduction occurs most often in a host’s red blood cells. Multiplication eventually causes red blood cells to rupture, and although most of the released parasites invade other red blood cells, a few develop in the bloodstream into male and female gametes. When ingested by a mosquito, these gametes mature into gametes and the sexual reproductive phase of the life cycle begins. Gametes undergo fertilization to produce zygotes. These eventually become sporozoites, the parasitic form that collects in the insect’s salivary gland, poised to infect the next host. On page 667 of this issue, Mair et al. (1) report the mechanism underlying the regulation of gene expression during the sexual cycle of this parasite.

The myriad of developmental events that any single organism experiences during its life is controlled by multiple levels of gene expression regulation. In multicellular eukaryotes, tissue- and developmental-specific regulation most often involves the hierarchical expression of diverse transcription factors that bind to specific DNA elements, thus activating or suppressing the expression of specific genes. Generally, in an early developing embryo, nuclear transcription—the synthesis of protein-encoding messenger RNA (mRNA) from genomic DNA—is very limited, and transcription-dependent mechanisms play a relatively minor role in modulating gene expression. By sequestering mRNAs into quiescent messenger ribonucleoprotein particles (mRNPs), translation of mRNAs into proteins is repressed. The release of translationally silent mRNAs from storage in mRNPs thus controls the timing and location of protein expression (2, 3).

Very little is known about the control of gene expression in *Plasmodium*, and the mechanisms underlying the activation of gamete maturation and fertilization have been complete mysteries. It has been known that two major female gamocyte mRNAs, P25 and P28, are translationally repressed (4, 5). That is, the female gamocyte stably stores these mRNAs and activates their translation upon ingestion by the insect. These transcripts encode unique *Plasmodium* proteins that appear to be necessary for parasite infection of the insect, though their actual functions remain unknown.

To identify the factors controlling translational repression in gametocytes, Mair et al. searched the gametocyte sex-specific suite of proteins, or proteomes, for those whose expression is up-regulated in the female gametocytes. The authors found DOZI, a protein with homology to the DDX6 family of RNA helicases. These enzymes catalyze the unwinding of an RNA helix (6). The DDX helicase family is closely linked to translational repression in many multicellular eukaryotes and in yeast, possibly by facilitating the binding of other proteins that repress translation.

To determine whether DOZI is associated with mRNPs in female gametocytes of *Plasmodium*, the authors generated a *Plasmodium* line expressing DOZI fused to green fluorescent protein (DOZI:GFP). This fusion protein localized to the cytoplasm of female gametocytes. Moreover, fluorescent in situ hybridization analysis of the p25 and p28 mRNAs revealed localization of both transcripts with DOZI:GFP in cells. DOZI:GFP could also be biochemically isolated in a complex with mRNPs that contained P25 and P28 transcripts.

Does DOZI function in the sexual development of *Plasmodium*? Mutant parasites that do not express the dozi gene develop normally in the asexual bloodstream stages and produce gametocytes and gametes, but do not develop fertilized zygotes. As predicted by the authors, the expression of p25 and p28 mRNAs was dramatically reduced in the dozi-null mutant, supporting the function of DOZI in storing translationally repressed mRNAs.

Like other eukaryotes, the malaria parasite stores maternal RNA in the female gamete for later use in directing early development. An RNA helicase is a key regulator of this process.

**Plasmodium gamocyte development.** Male and female gamocytes develop during bloodstream infections and mature to gametes within the mosquito gut. Female bloodstream gamocytes store translationally silent mRNAs in cytoplasmic bodies containing DOZI and activate the translation of these mRNAs in the insect. Female gametocytes are then able to develop into mature gametes and undergo fertilization.
repressed mRNAs. In addition, by microarray analysis, Mair et al. found that the expression of 370 other transcripts was also reduced in the DOZI-null mutant. Surprisingly, a large number of transcripts were also increased in abundance in the DOZI-null mutant. As the authors point out, these results suggest that the putative RNA helicase plays a critical role in maintaining steady-state levels of gametocyte-specific transcripts. This work further substantiates the phenomenon of translational repression in *Plasmodium* and its importance in regulating sexual development of these parasites. Given the widespread occurrence of translational repression and its role in both temporal and spatial gene expression, this should perhaps not be so surprising. The finding raises a number of provocative questions, however. How do translationally silent mRNPs undergo assembly-disassembly cycles? What triggers this process in the insect gut? When released from mRNPs, how do the once-silent mRNAs move from the cytoplasmic mRNPs to cytoplasmic polysomes for expression? The discovery that hundreds of mRNAs are influenced by the mutation of DOZI suggests that the putative helicase plays a pivotal role in control of sexual development in these important parasites. It may also be that closely related parasites, such as *Toxoplasma*, use a similar mechanism. The recent completion of several protozoan parasite genomes reveals a surprising lack of canonical transcription factors indicating that post-transcriptional mechanisms, like translational repression, may play a disproportionate role in gene regulation in these important pathogens. It may also be that closely related parasites, such as *Toxoplasma, Pneumocystis, Cryptosporidium*, and *Babesia*, may use a similar mechanism for regulating expression of their genes.

References

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**IMMUNOLOGY**

**Sugar Determines Antibody Activity**

**Dennis R. Burton and Raymond A. Dwek**

Antibodies come in many flavors to confront the bewildering array of pathogens to be encountered in one’s lifetime. At the structural level, this is achieved by an extensive variability in the sites that interact with foreign pathogen-associated molecules (antigens) that typically elicit an immune response. The remainder of the antibody molecule is much more conserved, as befits its primary role in binding to a limited set of effector molecules that control inflammatory responses and trigger antigen elimination. Differences in the amino acid sequences of conserved parts of the antibody molecule lead to different antibody classes [e.g., immunoglobulin G (IgG), IgA, IgM, etc.] and subclasses (e.g., IgG1 to IgG4 in humans) that bind different effector molecules. A new study by Kaneko et al. on page 670 of this issue (1) suggests that another type of difference between antibody molecules, determined by the sequences of attached oligosaccharides, may be crucial for antibody function. The results may have far-reaching implications for understanding antibody responses and provide further support for a critical role for glycosylation in immunity.

The IgG molecule consists of two Fab arms, involved in antigen binding, that are connected via a flexible hinge region to an Fc region, which binds to effector molecules (see the figure). The Fc region has two tightly interacting or paired Ig domains and also, in contrast, two domains that are separated and do not interact but have two oligosaccharide chains interposed between them. These chains cover the hydrophobic faces that would normally lead to domain pairing. The oligosaccharides are heterogeneous—about 30 structures, or glycoforms, are known, with certain residues being conserved and others highly variable. Differences in the sequences of the oligosaccharide chains lead to differences in orientation of the chains on the protein surface, spacing between the unpaired domains, and exposure of key sugar residues. In the three IgG structures shown (see the figure), one lacks terminal galactose and sialic acid on two arms of a sugar chain and exposes N-acetylglucosamine, one lacks sialic acid but places one of the terminal galactoses in a “pocket” on the Fc protein and the other in the interactional space between the two unpaired domains (this represents the predominant glycoform of IgG under normal conditions), and the third fully exposes terminal sialic acid residues.

The first indications that differences in glycosylation might affect antibody function came from studies associating rheumatoid arthritis with glycoform prevalence (2). The percentage of G0 glycoforms (no galactoses) is raised in rheumatoid arthritis, increases with disease progression, and returns to normal when patients go into remission. Pathology appears to result from interaction of exposed N-acetylglucosamine residues on the G0 glycoform with the manose-binding lectin, which subsequently activates a series of reactions (the complement cascade) in the blood with cellular destructive activities (3). Other studies have shown that the presence of fucose on Fc carbohydrate chains can influence binding of the IgG to Fc receptor molecules (4, 5). Fc receptor proteins are present on a variety of immune cells, and IgG binding can activate or inhibit inflammatory responses through respective Fc receptors (6). This control by sugar modification can be quite complex: A recent study (7) shows that human IgG-Fc receptor interactions depend upon sugar structures on both the Fc region of the IgG and on Fc receptors to permit discrimination of IgGs among Fc receptors.

Kaneko et al. focused on the role of sialic acids in the interaction of IgG and Fc receptors and in inflammatory responses in a number of mouse models. By lectin affinity chromatography, they enriched for monoclonal IgGs (even monoclonal antibodies are heterogeneous with respect to sugars) bear-

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