THE BIOCHEMISTRY OF ANTIGENIC VARIATION IN AFRICAN TRYPANOSOMES

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African trypanosomes cause sleeping sickness, a fatal disease of humans and domestic livestock in Africa. These protozoan parasites are related to *Trypanosoma cruzi*, which causes Chagas disease in Latin America. However, African trypanosomes have a very different way of evading their hosts' immune response than *T. cruzi*. *T. cruzi* avoids the immune response by entering several cell types of the mammalian host (*i.e.*, they become intracellular), whereas African trypanosomes are always extracellular and in constant contact with the immune system in the bloodstream. They manage to keep one-step-ahead of the immune response by periodically switching from expression of 10^7 identical copies of one variant surface glycoprotein (VSG) on their surface to expression of 10^7 identical copies of another immunologically distinct VSG – a phenomenon called antigenic variation. The surface VSG molecules constitute about 5% of the total protein of the organism. The recently sequenced African trypanosome genome revealed the presence of about 50 different VSG genes (*VSG*s) and more than 950 pseudo-*VSG*s in the genome, all of which are transcriptionally silent except for one. This active *VSG* is duplicated and translocated to one of about 20 potential *VSG* expression sites (ESs). Each of the 20 potential ESs is adjacent to a chromosomal telomere, but only one ES is actively transcribed in a given organism. The active telomere-linked ES is physically located in an extra-nucleolar body of the nucleus where it is transcribed by RNA polymerase I. Interestingly, some wild animals in Africa are partially resistant to African trypanosomes. In at least one case, the Cape buffalo, this resistance is not due the immune response, but due to an unusually high level of xanthine oxidase and a low level of catalase in the blood of infected Cape buffaloes, which results in excessive amounts of hydrogen peroxide, a reactive oxygen species that kills African trypanosomes. It is hoped that a knowledge of the African trypanosome genome and wild animal mechanisms for controlling African trypanosomes will ultimately suggest better ways to control or eliminate this deadly pathogen.