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Editorial

Testosterone and malaria infection

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Abstract

Males are in general more susceptible to infectious diseases than females that have been mostly ascribed to the immunosuppressive activity of testosterone (T). A convenient model to investigate T effects is Plasmodium chabaudi, the infectious agent of blood-stage malaria in the mouse, which shares several characteristics with P. falciparum causing malaria tropica, the most dangerous form of human malaria. Indeed, T induces susceptibility to blood-stage malaria with Plasmodium chabaudi in mice that manifests itself as a lethal outcome of otherwise self-healing infections.

Keywords: Gender; Malaria; Testosterone

The gender of hosts is known to be critical for the outcome of infectious diseases. In general, males are more susceptible than females which holds true for infectious diseases caused by viruses, bacteria, fungi, and parasites belonging to protozoans, helminths, and even arthropods [1]. Male susceptibility is often ascribed to be controlled by the male sex steroid hormone testosterone. Indeed, the previous data indicate a critical role of testosterone for the outcome of blood stage infections with the malaria parasite. Malaria is still a major public health threat that infects about 225 million people worldwide and causes 781,000 casualties per annum, mainly among African children in sub-Saharan regions [2,3]. An appropriate experimental model is the mouse malaria caused by *P. chabaudi*, which shares several common characteristics with the human pathogenic *P. falciparum* [4]. Blood stage malaria with *P. chabaudi* exhibits an extreme gender-dependence. Male mice succumb to infections, whereas females are able to survive the same infections [5]. This extreme gender-dependence has been unequivocally shown to be critically controlled by testosterone [6]. The role of T in malaria outcome has been already investigated at several different levels, and it therefore represents a most appropriate model to study T-effects on malaria.

Most remarkably, the suppressive lethal T-effect is not reversible, but persists after discontinuation of T-treatment for rather a long time [7]. This supports the view that T has the capacity to persistently reprogram expression of specific genes. The mechanisms whereby T could induce such reprogramming are completely unknown to date.

Researchers investigated T-induced reprogramming of gene expression in spleen and liver much more in detail and extent than done previously [6]. In particular, Dkhil et al. [8] identified those genes which are persistently deregulated by T and those genes which are normally responsive to malaria, but become persistently deregulated or even unresponsive to malaria after T-treatment. Moreover, some prominent gene candidates will be examined for possible epigenetic changes induced by T, to support the view of the T capability to reprogram gene expression, as it has been recently been described for T-dependent brain masculinization [9].

Efforts have concentrated on investigating T effects on the transcriptome-wide expression of mRNA, lincRNA (long intergenic non-coding RNA) and non-coding miRNA, as well as on the genome-wide DNA-methylation status of gene promotors as a presumable epigenetic regulator of gene expression [8]. They have used and developed newest biotechnologies, i.e., diverse microarray technologies such as Affymetrix microarrays, Agilent microarrays, miRExplore microarrays, and methylated DNA immunoprecipitation in combination with Nimblegen microarrays. Also, they showed that the action of T is more complex than hitherto assumed: There exist obviously intricate epigenetic regulatory networks controlling gene expression in spleen and liver as well as the outcome of *P. chabaudi* infections, which are apparently dysregulated by T. Conspicuously, the T-induced changes were much more pronounced in the liver than in the spleen, thus further corroborating our previous view that it is majorly the liver that mediates the suppressive effects of T against malaria [8,10]. Most spectacular is the finding that T may already affect the first line of pathogen discrimination, i.e., the recognition of pathogen-association molecular patterns through host pathogen recognizing receptors.

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