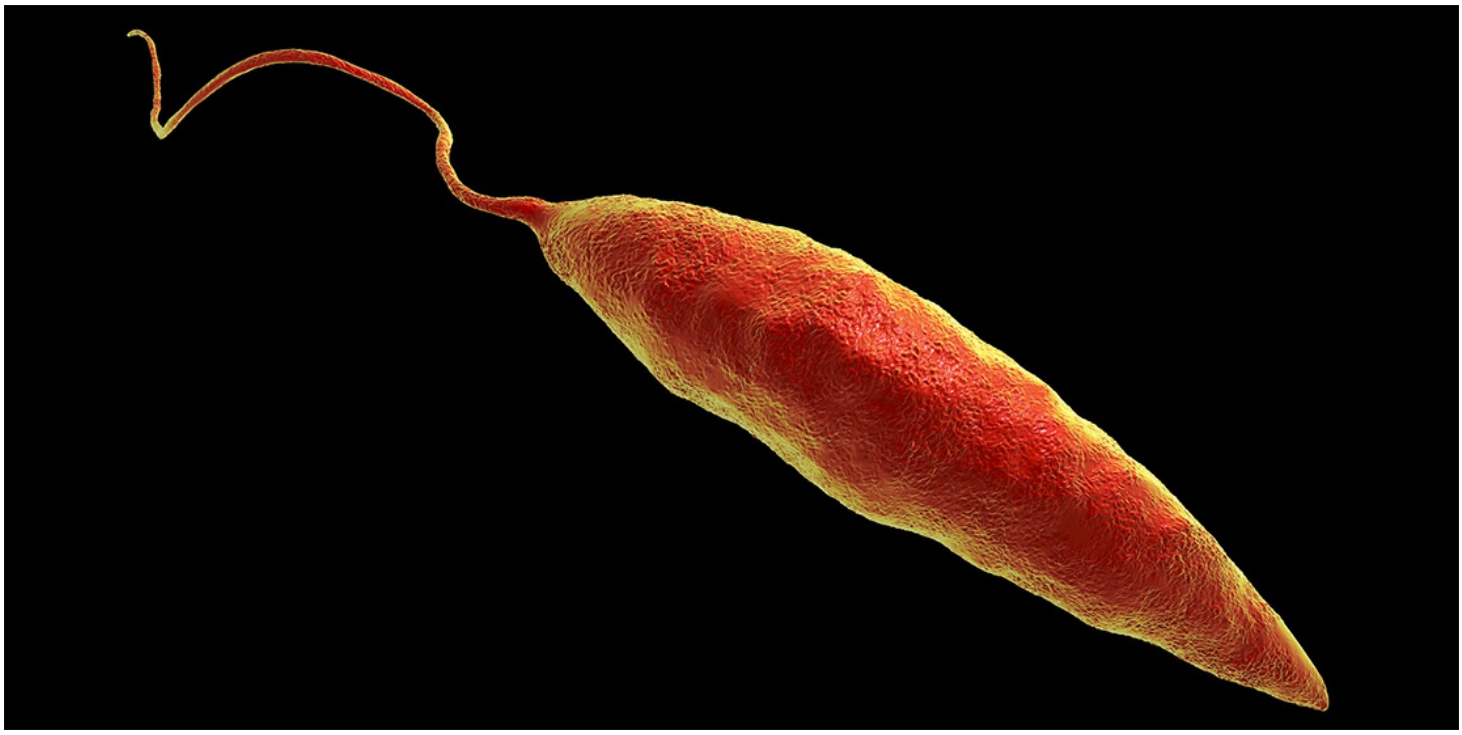
Chronicle of a drug resistance foretold

Tropical parasite was pre-adapted to drugs even before the treatment was discovered

27-04-18



Dit is de omschrijving

Visceral leishmaniasis, also called kala-azar, is a parasitic disease that kills 40,000 people every year, especially during outbreaks in the Indian sub-continent and East Africa. There are only a few drugs available to combat this scourge, but we may lose them because of parasite resistance. This phenomenon generally occurs when a drug is used in mass and parasites progressively adapt to it. This was not the case for antimonials, a group of drugs used to treat Leishmaniasis. Leishmania parasites in the Indian sub-continent were already pre-adapted to it, even before the discovery of the drug. Scientists of the Institute of Tropical Medicine (ITM) in Antwerp published their fascinating discovery in the journal *mSphere*.

Drug resistance is one of the biggest threats for scientists and health professionals working on infectious diseases. Bacteria, parasites and viruses are very clever and find numerous solutions to adapt to a drug used to kill them and ultimately develop resistance. "*As such, the days of any antimicrobial drug are numbered from the moment it is launched on the market. It is the start of an arms race, where scientists need to stay one step ahead of pathogens,*" said Prof. Jean-Claude Dujardin, head of ITM's Department of Biomedical Sciences. Scientists therefore need to understand why and how pathogens survive to a drug and draw lessons to make drugs even stronger next time.

How resistance normally occurs

Generally drug resistance occurs following a similar scenario. For several possible reasons, patients do not take the full treatment or receive a drug of lower quality, which creates ideal conditions for the survival of a happy few parasites. Then mutants start to appear in the population of parasite survivors. If mutation arises in a gene essential for the drug functioning, then the cells carrying this mutation are favoured and spread rapidly despite the drug pressure. Drug resistance is established and the pathogen has won…until the next round and the next drug comes along.

The wondrous case of pre-adaptation: the parasite emergency kit

In the case of antimonials and Leishmania from the Indian sub-continent, the scenario was rather different, as the ITM scientists describe in *mSphere*. Through their experimental work, the Belgian scientists saw that the majority of the parasites of the Indian sub-continent possessed a specific pre-adaptation to antimonials in the form of an emergency kit allowing the parasite to pump out the drug from its body. *"By matching this information with evolutionary data from a previous study*, we realised that all the parasites showing this pre-adaptation descended from a pre-adapted ancestor that arose in 1850,*" said Dr. Franck Dumetz, first author of the publication. "*The exceptional nature of this observation is that 1850 is much earlier than the discovery and first implementation of antimonials; it is even earlier than the discovery of Leishmania,*" added Dr Dumetz.

Possible explanations for pre-adaptation

According to the scientists, this unique pre-adaptation stems from an exposure of the parasites in question to another chemical agent that could have selected the creation of this emergency kit. They propose two explanations. On the one hand, groundwater in the Indian subcontinent naturally contains a high quantity of arsenic, a chemical element close to antimony and known to produce resistance across substances in Leishmania parasites (Perry et al. PNAS). On the other, pre-adaptation might have to do with the medical practice of the middle of the 19th century. In this period, Kala-Azar (black fever in Hindi) was not yet described as leishmaniasis, but considered by the British physicians as "quinine resistant malaria". They treated leishmaniasis with high doses of quinine, without success. Further work is in progress at ITM to elucidate the possible role of quinine in the development of the parasite's emergency kit that allowed it later on to survive to antimonials.

Prof Dujardin concluded: "*This pre-adaptation story is a lesson for us. For example, we need to check if local parasites do not show any pre-adaptation before launching a new drug, because it could ruin its long-term use. In the context of a neglected disease like leishmaniasis, we cannot take this risk.*"

END

Molecular Preadaptation to Antimony Resistance in Leishmania donovani on the Indian Subcontinent (Dumetz et al.)

http://msphere.asm.org/content/3/2/e00548-17

Notes to the editors:

- **(Imamura et al. eLife)*