How a protein variant could explain resistance to sleeping sickness drug

A specific variant of the surface protein VSG of African trypanosomes, the causative agents of sleeping sickness, is associated with resistance to the important drug Suramin. Scientists at the German Cancer Research Center have now been able to find a possible explanation for the formation of resistance based on the crystal structure of this protein variant.

Sleeping sickness is widespread in large parts of tropical Africa. The pathogens, African trypanosomes, transmitted by the tsetse fly attack the central nervous system and cause severe neurological disorders. Without treatment, the infection can lead to death.

For more than a hundred years, the drug Suramin, developed in Germany, has been used successfully against early stages of sleeping sickness. To date, there are only a handful of effective substances against the tropical disease, which is why the drug is on the WHO list of Essential Medicines. However, until now it was unclear how the drug actually reaches the inside of the pathogen and how it unfolds its efficacy there.

Scientists have now been able to generate trypanosome strains in the laboratory that exhibit a high level of resistance to Suramin. It turns out that the resistant strains all carried a particular variant of the so-called variable surface glycoprotein, called VSGsur. "This observation suggests that VSGsur is involved in the formation of Suramin resistance - however, we had no idea how this might work," says Erec Stebbins, a structural biologist at the German Cancer Research Center.

Using high-resolution studies of the protein's crystal structure, Stebbins was able to show that the VSGsur associated with resistance have a fundamentally different protein structure in a specific region than all other VSGs. This structural deviation allows the drug Suramin to bind to the VSGsur.

When the scientists genetically modified the deviant region of VSGsur, the trypanosomes again became sensitive to Suramin and the drug could no longer bind the VSG.

"We don't yet understand exactly how Suramin binding to VSGsur relates to resistance," Stebbins explains. "It's possible that VSGsur intercepts the drug, so that not enough Suramin reaches the inside of the pathogen. In any case, the results will help us better understand Suramin's action, which remains mysterious even after 100 years.

Until now, scientists had attributed a single function to the VSGs: they were considered to be a highly effective protective coat for the trypanosomes against the host's immune system: the unicellular trypanosomes are covered by a dense layer of identical VSGs, against which the infected person's antibodies are directed. This largely eliminates the parasites - until some of the pathogens switch to a different VSG gene - they have hundreds of them available. As a result, the surface proteins on the protozoa are completely exchanged and the trypanosomes masked in this way are no longer recognized by the antibodies. They multiply furiously, and the infection that the immune system had initially kept in check flares up again violently.

"The binding of Suramin shows us that the VSGs can have other, receptor-like functions beyond immune protection, which we now want to elucidate," Stebbins says.

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Structure of trypanosome coat protein VSGsur and function in suramin resistance

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Further information

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