Parasites persuade immune cells to invite them in for dinner, says new research

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The new findings may help scientists develop a vaccine against Leishmania infection.

The parasites that cause leishmaniasis use a quirky trick to convince the immune system to effectively invite them into cells for dinner, according to a new study published today in *PLoS Pathogens*. The researchers, from Imperial College London, say their findings improve understanding of the way *Leishmania* parasites establish an infection and could aid the search for a vaccine against this neglected tropical disease.

Leishmania parasites are transmitted by sand flies. After the parasites infect a sand fly, they make a sticky gel so that when the fly bites a human, it regurgitates this gel into the body. Today's research, which was funded by the Wellcome Trust, shows that the gel persuades immune cells known as macrophages to feed the parasites, rather than killing them.

Leishmaniasis is an infection caused by *Leishmania* parasites that affects around 12 million people per year, mainly in tropical and sub-tropical countries. Symptoms include disfiguring and painful skin ulcers and in severe cases the infection can also spread to the internal organs. Patients with the infection often suffer from social exclusion because of their disfigurement. There is currently no vaccine to protect against infection and although treatments are available, they are not always effective and access to drugs is limited in many areas.

Leishmania-infected sand flies carry the parasites in their midgut. The parasites produce a gel that turns into a plug, stopping anything from passing in or out of the fly's gut. The fly must regurgitate the gel plug before it can feed on human blood. When the fly bites a person, its barbed mouth parts tear the skin so when it regurgitates parasites along with the gel plug, the skin becomes infected.

Today's study shows that the gel's work doesn't stop there - it also helps the parasites to establish an infection by enticing macrophages to the bite site. Macrophages usually kill invading pathogens by eating and digesting them. However, according to the new research, the gel persuades macrophages to engulf the parasites and feed them rather than digest them. This happens within the first few days following infection, enabling the parasites to establish themselves and infect the skin.

Previous research suggested that the sand fly's saliva could be involved in manipulating the immune system. Today's study suggests that the gel has an even bigger effect than the saliva on establishing infection.

Dr Matthew Rogers, lead author of the study from the Division of Investigative Science at Imperial College London, said: "Leishmaniasis is a very debilitating disease, yet we know comparatively little about the way the parasites are transmitted by sand flies. This is because when scientists study the disease they usually inject the parasite into tissues

without including the gel or the sand fly's saliva. Our new research shows that we must consider the way the parasites enter the body - along with the gel and saliva - if we are to recreate infection and get an accurate picture of what is going on.

"Our new research shows that *Leishmania* parasites are very cunning - they make their own gel to control the human immune system so they can establish a skin infection. There is more work to be done here - our previous work in mice has suggested that injecting a synthetic version of the gel into people might provide them with some protection against infection and we would like to explore this further," added Dr Rogers.

The researchers looked at *Leishmania* infection in mice and found that the gel, called promastigote secretory gel (PSG) enticed macrophages to the site of entry. They compared the effect of PSG with the effects of saline and sand fly saliva on the number of macrophages recruited to a bite site, 4-72 hours after the bite. In the experiment, PSG recruited 108 times more macrophages to the bite than saline and five times more than sand fly saliva.

The researchers also found that PSG persuaded macrophages to feed, rather than kill, the parasites. When macrophages want to kill a pathogen, they produce nitric oxide. However, the researchers' experiments showed that PSG influences the immune cells to produce food, in the form of polyamines, for the parasites instead.

Finally, the researchers looked at the effect of PSG on parasite survival in vitro. They infected macrophage cells with *Leishmania* parasites with and without PSG. They found that more parasites survived in the first 48 hours following infection when PSG was added; both the proportion of infected cells and the number of parasites in the cells increased by up to 8-fold with PSG. The parasite infection declined after 48 hours in cells both with and without PSG, suggesting an early window of time in which

PSG helps the parasites establish an infection.

More information: www.plospathogens.org/home.action

Source: Imperial College London (news : web)