Science in Synch

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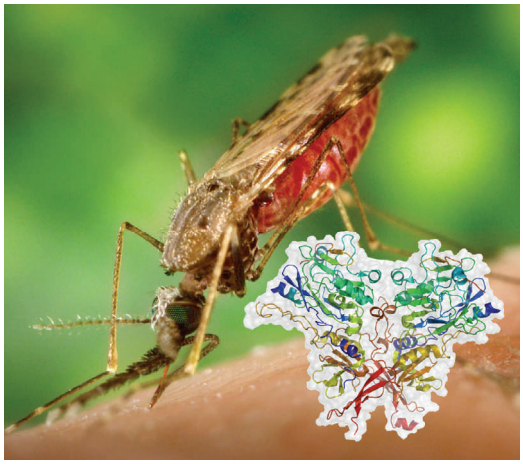
Illuminating a parasite invasion

The human body is a perfect home for many parasites that seek out the nutrient-rich shelter of a host, with the invader playing a game of hide and seek with the host's immune system until they can find the cells that are just right for the parasite to occupy, eventually causing sickness. Some of the nastiest parasites with respect to human health are known as apicomplexans. Of these, the most notorious are the malaria-causing *Plasmodium* and *Toxoplasma gondii*, which is responsible for toxoplasmosis. University of Victoria professor Martin Boulanger has been using the Canadian Light Source to unlock the detailed mechanisms of how *Toxoplasma* parasites gain access to the hospitable environment within a host's cells. The findings of their collaborative work with the Lebrun lab in France and published in *Science,* could lead to new treatments for toxoplasmosis, malaria and numerous other diseases caused by apicomplexans.



Mosquitoes carry and transmit the apicomplexan parasite *Plasmodium*, causing malaria in humans. Apicomplexan parasites use a complex made of the AMA1 and RON2 proteins (inset) to invade host cells undetected. *Source: Tonkin et al., 2011*

Apicomplexan parasites enter the human body and selectively scan for the most suitable host cells to invade. Interestingly, these parasites can't survive outside of the host cell, and have developed sophisticated mechanisms to gain entry into a host cell without drawing the attention of the host's immune system. To do this, the parasite establishes a protein complex comprised of AMA1 (for apical membrane antigen 1) and RON2 (rhoptry protein 2) that anchors a ring-like structure on the surface of the host cell known as the Moving Junction Complex (MJC). The parasite then actively propels itself through this ring without killing the host cell, akin to passing a needle through a balloon without popping it.

"The RON2 protein is injected from the parasite into the host cell and resurfaces through the host cell's membrane with an exposed region waiting to bind with AMA1 on the parasite's cell surface." explains Boulanger.

It turns out that a structural cornerstone of the MJC comes about through one of the research team's discoveries. "The interaction between AMA1 and RON2 results in an unexpected and substantial structural reorganization that enables the two proteins to form an intimate and extensive structure," explains Boulanger. "This complex is strong enough to withsrand the shear forces associated with the parasite propelling itself through the constricted MJC ring and into the host cell."

Understanding the MJC's structure will be instrumental in designing therapies that can attack the two proteins before they have a chance to fuse, slamming the door on the parasite.

Fast facts:

- Apicomplexan parasites are responsible for a number diseases that gravely impact humans, including malaria and toxoplasmosis.
- The parasites are able to latch onto and invade a host's cells by using two proteins to build a structure called a moving junction complex. The complex acts like a tunnel for the parasite to inject itself into the cell without triggering the host's immune system.
- Understanding and preventing the formation the moving junction complex could lead to therapies that may prove effective against all apicomplexan parasites.

Reference:
Tonkin et al., 2011. Host Cell Invasion by Apicomplexan Parasites: Insights from Co-structure of AMA1 with a RON2 peptide. ***Science 333****, 463 (2011),* DOI: 10.1126/science.1204988

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The AMA1-RON2 co-structure that makes up the MJC also appears to be shared by an otherwise highly diverse group of parasites. The formation of one formula that could prevent infection is much easier than finding recipes to attack possible weaknesses in each individual parasite species.

Boulanger and his colleagues are now back in the lab with more proteins to analyze and they have picked up a new partner along the way in the Vancouver-based Centre for Drug Research and Development. The partnership with the CDRD will be based on developing small molecule therapies that could be used to combat the parasites and the devastating diseases they cause.

“If they are all invading using this mechanism and if you can disrupt this interaction, this structure could prove to be the Achilles’ heel for these parasites,” Boulanger says.

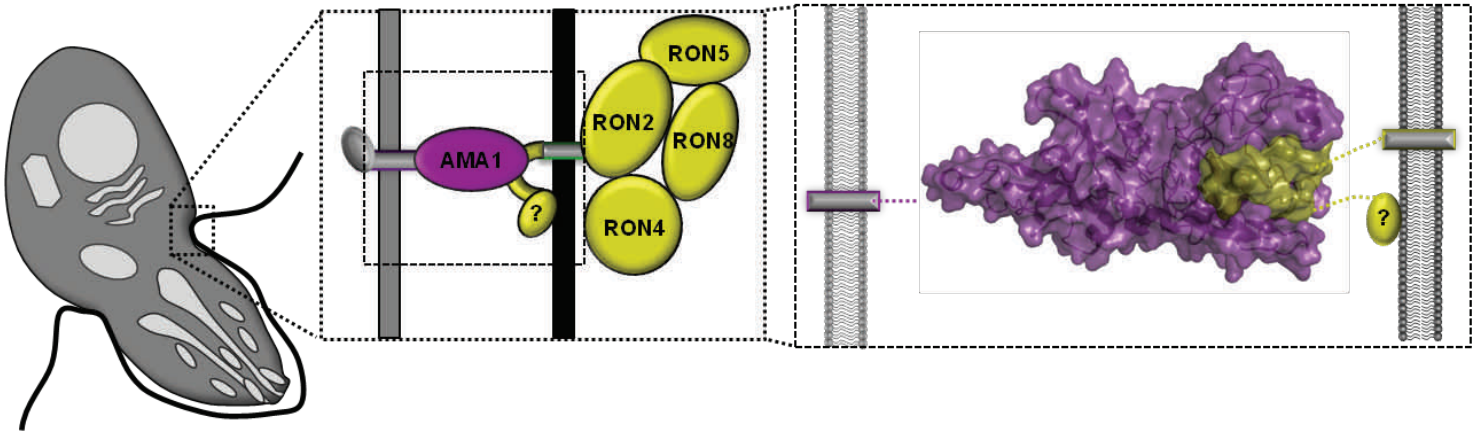

Illustration of how the apiccomplexan parasite *Toxoplasma gondii* uses the moving junction complex made of AMA1-RON2 proteins to invade a target host cell. The moving junction complex acts as a bridge that enables the active parasites to enter the host cells undetected.
Source: Tonkin et al., Science, 2011