How mice survive infection by virulent Toxoplasma parasites

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This is a laboratory mouse. Credit: Roberto Keller, IGC.

One of the commonest parasites in the world is *Toxoplasma gondii*. *Toxoplasma* can infect most warm-blooded animals, including humans, and causes significant damage to the unborn child if a woman becomes infected for the first time during pregnancy. The natural cycle of the organism depends on cats and on mice. Infection by *Toxoplasma* normally doesn't kill the animal, but there are some "virulent" strains that

kill mice only a few days after infection. Jonathan Howard, researcher at the Institute for Genetics, University of Cologne (Germany) and at the Instituto Gulbenkian de Ciência (IGC; Portugal), and his team have now found a mechanism that allows some mice to survive infection by the virulent strains. These findings offer an explanation for the evolution of parasitic strains with different levels of virulence. This study was published today in the open-access journal *eLife*.

The sexual reproduction of this parasite occurs only in cats and result in the release of enormous numbers of *Toxoplasma* eggs in their feces. These get eaten by grazing animals such as sheep or chickens but also by small wild animals such as mice. Upon infecting these animals, the parasite normally settles down in cysts in brain and muscle and can wait for many months until another animal eats its host. When mice are eaten by a cat the *Toxoplasma* completes its cycle. In the case of virulent strains of *Toxoplasma*, the outcome of the infection results in the rapid death of the mouse which can be bad for the parasite, because if the mouse dies from the infection before being eaten by a cat the parasite cannot complete its cycle and is eliminated. Virulent strains should therefore be at a disadvantage and die out. But the presence of these virulent strains in nature show that somehow there must be a mechanism to keep them.

The story depends on the balance that needs to be reached between the virulence of a parasite and the resistance of its host, if both parties are to survive. If the resistance is too weak, the host dies rapidly. When laboratory mice are infected with a non-virulent strain of *Toxoplasma* a group of proteins from the immune system of the mouse, the IRG proteins, disrupt the intracellular vesicles where parasites are located, killing most of them and saving the mouse's life. The surviving parasites become dormant as cysts in brain and muscle. Virulent parasites inactivate the IRG proteins of laboratory mice, which therefore die of the infection. Howard's team discovered that IRG proteins from many

strains of wild mice differ from the laboratory strains, and cannot be inactivated by virulent strains. These wild mice are extremely resistant to virulent *Toxoplasma* strains. The high resistance of the mouse balances the high virulence of the parasite. As a result, the infected mice survive long enough for the parasites to make cysts and survive in a dormant state, allowing time for the mouse to be caught and eaten by a cat, and therefore for the parasite to be propagated.

Jonathan Howard explains these findings in the light of evolution: "We think there is probably a kind of arms race going on out there. *Toxoplasma* needs to infect mice efficiently because they are such good vectors to cats, but mice have exploited IRG proteins to create a resistance mechanism. The better the IRG resistance mechanism, the stronger the *Toxoplasma* virulence mechanism has to become. But why are not all mice as resistant as possible? We suspect that maintaining a highly resistant IRG system might be costly for the individual, though we do not know why. In fact, the IRG system has disappeared in several vertebrate groups perhaps because they are not important vectors for *Toxoplasma*. The maintenance of the highly developed IRG system in the mouse probably tells us that this species is an evolutionarily significant host for *T. gondii*."

More information: Lilue, J., Muller, U.B., Steinfeldt, T. and Howard, J.C. Reciprocal virulence and resistance polymorphism in the relationship between Toxoplasma gondii and the house mouse. *eLife* 2013;2:e01298. dx.doi.org/10.7554/eLife.01298

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https://phys.org/news/2013-10-mice-survive-infection-virulent-toxoplasma.html