Scientists discover how deadly fungal microbes enter host cells

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A research team led by scientists at the Virginia Bioinformatics Institute (VBI) at Virginia Tech has discovered a fundamental entry mechanism that allows dangerous fungal microbes to infect plants and cause disease. The discovery paves the way for the development of new intervention strategies to protect plant, and even some animal cells, from deadly fungal infections. The findings are published in the July 23 edition of the journal *Cell*.

The researchers have revealed how special disease-related proteins, known as effectors, blaze a trail into cells. Fungi and fungal-like microbes known as oomycetes produce effector molecules that penetrate cells and switch off the host's defense system. Once the host's immune system has been disabled, the fungus or oomycete swiftly follows up, breaking and entering the cell and unleashing disease.

The pathogens in question, which include the microbe that caused the Irish potato famine in the nineteenth century, cause billions of dollars of losses for commercial farmers worldwide in crops such as soybean. They are also responsible for potentially fatal infectious diseases in humans.

Said Brett Tyler, professor at VBI and the leader of the project, "Our breakthrough finding is that these dangerous disease-causing proteins must bind a specific lipid molecule found on the cell surface before they can enter the cell."

In a previous study, Tyler and other researchers had pinpointed specific

regions of the effector proteins that are intimately involved in breaking and entry of the cell. The new study shows that these regions on the effector proteins bind the lipid phosphatidylinositol 3-phosphate and that this binding is essential for the proteins to enter the cells. Adds Tyler, "The nasty proteins enter by hitching a ride on a lipid raft, a region of the cell's outer membrane that can be internalized by the cell. The lipid acts as a bridge between the effector protein and the raft, and in doing so help to unlock the door for entry of the disease-causing proteins into the cell."

Intriguingly, the researchers have also identified two methods to block the entry process that could lead to new disease interventions against infection in medicine and agriculture. Shiv Kale, a graduate student at VBI and one of the lead authors on the study, remarked: "We were able to block the entry process of the disease-related proteins using two types of inhibitors. The first group of inhibitors covers the lipid so that the pathogen cannot get access to it. The second jams the site on the protein that normally binds the lipid."

The scientists were also able to show that the entry process into some human cells takes place by the same mechanism. Said VBI Associate Professor Chris Lawrence, who collaborated on the study, "Our finding that the entry of the effectors into human cells can be blocked with small molecules suggest that it may be possible to find new strategies to combat several debilitating human diseases, in addition to treating plant diseases."

More information: Kale S, Gu B, Capelluto DGS, Dou D, Feldman E, Rumore A, Arredondo FD, Hanlon R, Fudal I, Rouxel T, Lawrence CB, Shan W, Tyler BM (2010) External lipid phophatidylinositol 3-phosphate mediates entry of eukaryotic pathogen effectors into plant and animal host cells. *Cell* 142(2) In press. Available online at www.cell.com/current

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