Microbiology: On the trail of bacterial saboteurs

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A previously unidentified bacterial protein variant gums up the gears of a last-resort cellular suicide mechanism

Pathogenic bacteria that successfully penetrate the interior of a cell find themselves living on borrowed time before the infected cell self-destructs via the programmed cell death mechanism known as apoptosis. However, certain pathogens are able to protect themselves by producing cell death-delaying factors that target the mitochondria, key metabolic organelles within the cell that also represent 'ground zero' for the onset of apoptosis.

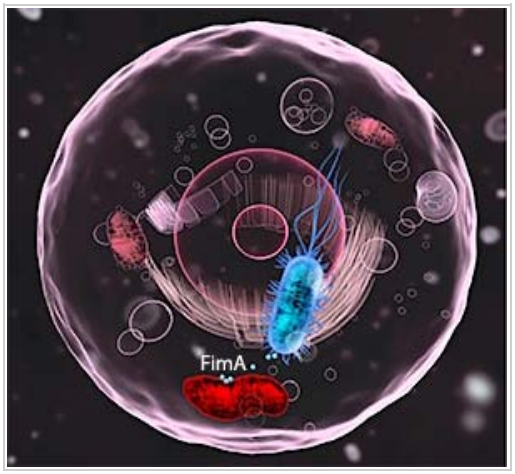

Fig. 1: Shortly after infecting a cell, the pathogenic bacterium, *E. Coli* K1 (blue), releases a soluble variant of the FimA protein, which binds to mitochondrial surfaces (red) and thereby blocks the onset of cell death.

The identity of these anti-apoptotic molecules has remained a mystery, but new research from a team led by A*STAR Institute of Molecular and Cell Biology and National University of Singapore researcher Victor Yu has now uncovered a surprising culprit[1]. After screening soluble proteins produced by *Escherichia coli* K1, a pathogen responsible for neonatal sepsis and meningitis, postdoctoral fellow Sunil Sukumaran identified the protein FimA as the most likely candidate apoptotic inhibitor. "FimA is known to be a component of the bacterial pili, which is a structure useful for adhesion to host cells and other substrates," explains Yu. "Hence, FimA was not known to be a soluble protein."

Nevertheless, the researchers observed clear evidence of FimA localization at host cell mitochondria within an hour of infection (Fig. 1); similar findings were also observed with other disease-causing, FimA-expressing bacteria such as *Salmonella* or *Shigella*. FimA was largely no longer associated with mitochondria by 12 to 14 hours post-infection, which is when infected cells normally begin to undergo apoptosis.

Bacterial FimA appears to exert its anti-apoptotic effects by binding to the mitochondrial voltage-dependent ion channel-1 (VDAC1) and subsequently stabilizing its interaction with the hexokinase (HK) protein. "Many cancer researchers already have data suggesting that the VDAC–HK complex plays an important role in turning off the suicide program in cancer cells," says Yu. "This work may therefore offer new insights into the role of these pathogens in promoting cancer of the gut, such as stomach and colon cancers."

Although Yu and his co-workers examined only a handful of bacteria species in this study, FimA is ubiquitously expressed among many other pathogenic bacteria residing within the human gut. Yu suggests that at least some of these are likely to employ a similar mechanism, and hopes to more closely characterize the production and activity of soluble FimA in future animal studies. "It would also be very useful if we could find small molecular-weight compounds for probing the mechanism of action of FimA–VDAC–HK, and explore their potential as drug candidates for treating cancers and infectious diseases caused by pathogenic bacteria in the human gut."

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The A*STAR-affiliated researchers contributing to this research are from the Institute of Molecular and Cell Biology and the Institute of Medical Biology

Reference

1. Sukumaran, S.K., Fu, N.Y., Tin, C.B., Wan, K.F., Lee, S.S. & Yu, V.C. A soluble form of the pilus protein FimA targets the VDAC-hexokinase complex at mitochondria to suppress host cell apoptosis. *Molecular Cell* 37, 768–783 (2010). | article

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