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Molecular mechanism of selected autophagy elucidated

Intestinal cell defence mechanism against bacteria

FRANKFURT. Salmonella is widely prevalent in the animal kingdom. The reason we do not suffer from severe intestinal infections very often is due to our body's defence system, which manages to digest invading bacteria. This is why, generally speaking, a healthy human being will only fall ill if he consumes more than 100.000 salmonella bacteria via a contaminated food source, such as eggs or meat. An international team of researchers, led by Prof. Ivan Dikic from the Goethe University in Frankfurt has now found out how body cells recognise salmonella and render it harmless. Understanding this process at a molecular level is crucial in identifying new targets for treatment. Tropical and sub-tropical countries in particular, where various sub-species of salmonella are common, are experiencing a rapid increase in resistance to antibiotics, with children at greatest risk.

Salmonella infection begins with bacteria entering the epithelial cells of the intestinal mucosa. To prevent them multiplying there, special cell organelles, called autophagosomes are activated. These encircle the invaders and then become absorbed in other organelles – lysosomes – that contain certain special digestive enzymes, which break down the bacteria into their constituent parts. But how exactly do the autophagosomes recognise salmonella? Prof. Ivan Dikic and his research group at the Biochemistry Institute II have now shed light on this mechanism.

As reported in a current article in the scientific journal "Science", the salmonella are marked as 'waste material' by the molecule ubiquitin. In order for the autophagosomes to become active, the marked bacteria have to bind to another molecule – LC3 – on the autophagosomal membrane. Here, the protein optineurin plays a key role, linking the marked Salmonella to the autophagosomal LC3, thereby setting off a process of selective autophagy. But optineurin becomes active as a link only after being chemically modified by an enzyme, (in this case it is phosphorylated by the protein kinase TBK1). "We suspect that phosphorylation acts as a regulated switch to trigger selective autophagy of bacteria but might also prove significant in other cargoes like protein aggregates or damaged mitochondria" explains Prof. Ivan Dikic, underlining the importance of these findings. It is thought that impaired autophagy processes may be implicated in, among other things, the development of cancer as well as neurodegenerative diseases.

In the area of infectious diseases, these findings are particularly relevant in view of the fact that gastrointestinal disease caused by Salmonella enterica has rapidly increased since the mid-1980s. In Germany, approx. 30,000 cases were reported to the health authorities in 1985, but by 2005 the figure has risen to 52,000. Worldwide, 94 million people fall ill each year with acute gastroenteritis, and 155,000 of these die. Typhoid, a disease also caused by Salmonella, affects 16 million people annually and mortality rates reach 200,000, with children in particular falling victim to the disease. Bacteria are becoming increasingly resistant to antibiotics so that the potential for treating disease is limited. Chloramphenicol, a formerly popular broad-spectrum antibiotic, is now ineffective, and even Fluoroquinolones, currently a commonly prescribed antibiotic, is proving inadequate in fighting bacteria. As co-author Prof. Dirk Bumann from the Biozentrum at Basel University puts it: "There is a pressing need to find new forms of treatment for infectious diseases. A better understanding of how the body's own defence mechanism makes use of autophagy will certainly help."



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Die Goethe-Universität ist eine forschungsstarke Hochschule in der europäischen Finanzmetropole Frankfurt. 1914 von Frankfurter Bürgern gegründet, ist sie heute eine der zehn drittmittelstärksten und größten Universitäten Deutschlands. Am 1. Januar 2008 gewann sie mit der Rückkehr zu ihren historischen Wurzeln als Stiftungsuniversität ein einzigartiges Maß an Eigenständigkeit. Parallel dazu erhält die Universität auch baulich ein neues Gesicht. Rund um das historische Poelzig-Ensemble im Frankfurter Westend entsteht ein neuer Campus, der ästhetische und funktionale Maßstäbe setzt. Die „Science City“ auf dem Riedberg vereint die naturwissenschaftlichen Fachbereiche in unmittelbarer Nachbarschaft zu zwei Max-Planck-Instituten. Mit über 55 Stiftungs- und Stiftungsgastprofessuren nimmt die Goethe-Universität laut Stifterverband eine Führungsrolle ein.

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