

A paradigm shift in immune response regulation

The discovery of a new signalling pathway may provide a target for structure-based drug design

Abstract:

Over the past decade various pieces of the puzzle how signal transmission controls immunity have been coming together. Now, in “Cell” an international team reports a paradigm shift in the regulation of immune response. Their results show that interaction with a linear ubiquitin chain is crucial for nuclear factor kappa B activation. Their findings may also contribute towards structure-based drug design to target the defective NF- κ B pathway in diseases such as cancer, inflammation and immunodeficiency.

The body's first line of defence against bacteria and viruses is the innate immune system where phagocytes identify the foreign organism and initiate an alarm reaction, often accompanied by inflammation. As a consequence, molecular cues are produced in the blood, such as Tumor Receptor Factors (TNF) or interleukin-1, and these stimulate further reactions in the immune system. But what exactly happens after the molecular cues have docked onto the cell receptors that specialize in immune response? What is the basis of signal transmission from the cellular receptors into the cellular interior? Over the past decade, the overall picture of this large puzzle has been gradually pieced together to show that modifications in the cell protein - including the addition of phosphate groups (phosphorylation) or the conjugation of small modifier ubiquitin (ubiquitination) - play a central role in controlling the immune system.

Scientists at Frankfurt's Goethe University led by Prof. Ivan Dikic have established an international collaboration to investigate the role of ubiquitin modification in these pathways. The international team includes the laboratories of Soichi Wakatsuki (Photon factory, Tsukuba, Japan), Fumiyo Ikeda (MedILS, Split, Croatia), Felix Randow (LMB, Cambridge, UK) and David Komander (LMB, Cambridge, UK). They have been investigating how a transcription factor known as the nuclear factor kappa-B (NF- κ B) coordinates the gene expression necessary for the cell's immune response. NF- κ B is activated by an enzyme (IkappaB-Kinase, IKK) with a regulatory subunit that brings to mind the mysterious captain in Jules Verne's science fiction novels: NEMO.

The question that had to be answered was how does NEMO activate NF- κ B? This is where the work of the Frankfurt biochemists came in. They identified a subdomain of NEMO, called UBAN that binds selectively to a specific type of ubiquitin. This protein is ubiquitous in the cell and has various functions, acting as a multifaceted molecular signal. It can function as a single molecule (monoubiquitin) or in the form of chains (polyubiquitin).

In the scientific journal “Cell”, Ivan Dikic and his colleagues report that NEMO specifically binds to linear ubiquitin chains and that this is an essential step for NF- κ B activation. This came as a big surprise to the team, since it was previously thought that other types of ubiquitin signals were critical for NEMO-dependent NF- κ B activation.

“This results in a paradigm change”, says Ivan Dikic, “it means, that current knowledge on NF- κ B activation and the role of linear ubiquitin chains needs to be updated”.

In cooperation with the group of Soichi Wakatsuki, NEMO’s structure could be solved. The work demonstrates that the UBAN domain binds to a linear ubiquitin chain according to the key-and-lock-principle. “These new findings not only explain the atomic details of ubiquitin chain selectivity, but can also provide useful insights into developing therapy for targeting the NF- κ B pathway”, reports Soichi Wakatsuki. Increased activation of the NF- κ B pathway is known to be linked to development of different diseases such as cancer and inflammation.

The discovery also has direct medical relevance. “We are happy that this basic scientific discovery may explain the detrimental effect of NEMO mutations in patients suffering from X-linked ectodermal dysplasia and immunodeficiency”, Ivan Dikic points out. Ectodermal dysplasia is a hereditary disease, which affects 1-5 children in 10,000 newborn children. It causes the skin to be very thin and the perspiratory glands to malfunction. In some cases it is combined with immune deficiency. The molecular defect is a mutation in the NEMO gene, which blocks the activation of the NF- κ B pathway in epidermal and immune cells.

Information: Prof. Ivan Dikic, Institute for Biochemistry II, Tel.: +49 69 6301 4546;
ivan.dikic@biochem2.de.

This work will be published in the March 20, 2009 issue of the scientific journal “Cell” published by Cell Press, USA.

The Goethe University, with its strong research focus, is based in Frankfurt, Europe's financial metropolis. It was founded 1914 by Frankfurt citizens and is now one of Germany's ten largest universities. On January 1, 2008 it returned to its historical roots as a university financed by foundations, guaranteeing it an exceptional degree of autonomy. The historical ensemble of buildings designed by Hans Poelzig back in the 1920s in Frankfurt's Westend is now the hub of what, when complete, will be Germany's most beautiful campus - the construction work will cost a total of about EUR 600 million. Since 2000, over 50 new foundation-financed professorships and visiting professorships have been established, meaning the Goethe University is again a trailblazer in Germany, and has been well up with leaders for three consecutive issues of the CHE's three research ranking table and the German Academic Excellence Initiative.