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EDITORIAL

Decrypting the labyrinth of inflammatory cell signaling pathways

Editorial to the meeting "Inflammation 2010"

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Following the tradition since 1998, the "Inflammation 2010" meeting was organized again in Luxembourg and gathered more than 550 scientists and exhibitors. The gorgeous, brand-new Conference Centre Kirchberg opened its doors for the first time to honor the guests of the "Inflammation 2010" meeting. Besides the enthusiastic talks and discussions, more than 200 posters created an intense atmosphere with the newest research results in cell signaling, cancer, inflammation, apoptosis and innate immunity. Thanks to the more than 50 plenary speakers, we are again one step closer to decrypt the labyrinth of signaling pathways.

Over centuries, inflammation has been linked to diseases and an aspiration to discover the principles behind this connection had motivated scientists better understand the underlying mechanisms. At the present time, our knowledge is quite advanced about signaling pathways that are used by cells to ensure physiological functioning on one hand, but that are misused to trigger initiation and progression of cancer on the other hand. However, despite considerable knowledge, we are still far away from the finishing line.

It is well known that external or internal signals are converted and transmitted within a cell by the action of various enzymes, mostly kinases, in order to correctly respond to changes in the cellular environment. Indeed, errors in this signal transduction cascade may lead to chronic human diseases, including diabetes, autoimmune diseases and cancer. These disorders have one in common: they are all linked to inflammation. To know which enzymes are involved in cell signaling and to understand in detail how these pathways work is the prerequisite for the development of novel drugs effective against inflammation and resulting diseases.

The highly coordinated orchestra of signaling pathways, including numerous molecules and biochemical events, performs its functions constitutively or upon activation in each single cell. Understanding the crosstalk between them and how deregulation of one pathway may affect a second one are fundamental for the investigation of this machinery of life that regulates cellular trafficking.

Trying to untwist the cobweb of signaling molecules and to identify 'who regulates whom' reminds the philosophic question: "Which came first, the chicken or the egg?" Inflammation 2010 brought light into this dilemma and uncovered interesting correlations between signaling molecules and principles applied to inflammation.

We do not need to emphasize that one of the key players in inflammation signaling is the transcription factor NF-κB. It plays important roles in immunity, anti-apoptosis, proliferation and activation of target genes involved in tumor promotion, angiogenesis and metastasis. Moreover, NF-κB is a mediator of inflammatory diseases and cancer, and has been shown to induce resistance to various chemotherapeutic agents. Besides well-known facts about the classical NF-κB pathway, new evidence about the crosstalk between RelA and RelB in the nucleus, which are the main components of canonical and alternative pathway, respectively, was presented. Moreover, recent results suggest the role of RelB in the control of cell growth and tumorigenesis through positive regulation of the tumor suppressor gene p53. According to Véronique Baud

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(Institute Cochin-INSERM U567, Paris, France), it seems that RelB constitutively binds to the p53 promoter thereby regulating its expression and exerting anti-tumor activity.

Altogether, these findings indicate that the RelB/p50 DNA binding inhibition by RelA abrogates the positive function of RelB as a cellular growth repressor. This new insight surprisingly shifts the attention to novel anti-cancer therapies based on RelB activation rather than inhibition.

Of particular interest is also the role of the intracellular ubiquitin-editing protein A20 in the negative feedback regulation of NF-κB signaling presumably as a de-ubiquitinating enzyme. Recent studies by the team of Rudi Beyaert (Gent University, Belgium) demonstrate that specific A20-binding proteins are able to target A20 to ubiquitinated substrates in the NF-κB signaling pathway.

Furthermore, growing evidence indicates the close connection between antioxidant signaling pathways and inflammation. Recent data obtained by the research lab of Pr Young-Joon Surh (Seoul National University, Korea) revealed a crosstalk between NF-κB and redox-sensitive transcription factors, including, amongst other, Nrf2, which plays a key role in regulating antioxidant gene induction and moreover affects inflammation. Cysteine thiols present in those transcription factors and their regulators act as redox-sensors, thereby adjusting transcriptional regulation of many genes involved in the maintenance of cellular homeostasis. This may provide a unique strategy for molecular-target based chemoprevention simply by modifying thiol groups by oxidation or covalent modification. Although NF-κB is admittedly a main actor in inflammation, it is definitely not the only one.

Similarly, the German team of Pr Mathias Gaestel (Hannover Medical School) showed that MAPK-activated protein kinases (MKs), signaling molecules downstream to p38 MAPK-α, are also implicated in the inflammatory processes. Especially, MK2 and MK3 have been shown to be promising novel drug targets. Inhibitors of these kinases are not only highly potent in the prevention of inflammation but also possess anti-carcinogenic properties, confirmed by experiments with MK2 knockout mice that did not develop multistep skin tumorigenesis. Due to their high specificity/selectivity, such inhibitors might be used in the future as combined novel oral anti-inflammatory and anti-carcinogenic drugs.

Likewise, much discussion was dedicated to another important family of proteins involved in inflammation—cyclooxygenases—enzymes acting in the prostaglandin biosynthesis. One of the family members, COX-2, is thought to be involved in the inhibitory control of the mucosal immune system against the normal, pivotal gut flora. Indeed, COX-2 is constitutively expressed at high levels in colonic mesenchymal stem cells. But instead of being activated through microbes, convincing data have been reported that the up-regulation of COX-2 expression arises from mRNA stabilization downstream of fibroblast growth factor FGF9, which makes FGF9 an important player for COX-2 expression regulation that might be responsible for its constitutive expression *in vivo* as demonstrated by the team of Stappenbeck (Washington University in St. Louis, USA).

Nevertheless, COX-2 is not only up-regulated during inflammation but is also found constitutively expressed in different adherent tumors. Due to this observation, selective COX-2 inhibitors seem to be promising anti-cancer agents. However, Dr Claudia Cerella (LBMCC, Luxembourg) surprisingly found that these inhibitors prevent the induction of apoptosis by commonly used chemotherapeutics in COX-2 expressing leukemia cells. These unexpected results are very important in the light of using anti-inflammatory agents as chemoadjuvants during treatment of such tumors.

Another issue was dealing with the well-investigated Notch pathway, which is implicated in angiogenesis and ensures the regulation of cell fate decision in neuronal and cardiac cell development as well as in vascular morphogenesis. So far, its implication in vascular epithelial cells upon inflammation was unknown.

During the congress Charreau and colleagues (Université de Nantes, France) presented data demonstrating that the inflammatory cytokine TNFα leads to an induction of Notch2 and a decrease in Notch4 expression. As a consequence of such an impaired Notch4 expression endothelial cell dysfunction and transplant arteriosclerosis are promoted in cardiac allograft vessels, which finally results in graft ischemia and allograft rejection. Notch2 activation on the other hand has been shown to induce caspase-dependent apoptosis by modulating the transcription of some specific pro- and anti-apoptotic proteins. Taken together TNFα may lead to cell death by the functional replacement of protective Notch4 by Notch2.

In conclusion, understanding the connections between different signaling pathways brings us closer to understanding the complete picture due to which medicine will become in the future the science about the prevention of diseases rather than about their healing.

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January 25–28, 2012
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