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Biomedical Sciences Research Center

PRESS RELEASE

Novel insights on Tumor Necrosis Factor (TNF) physiology lay the ground for safe and effective cancer treatments

40 years after the original findings that granted its name, Tumor Necrosis Factor (TNF) reappears in the forefront offering new potential for safer medical applications in curing cancer, corroborating its original characterization.

Vari, May 15 2013. In the late 19th century, the physician and surgical oncologist William B. Coley managed to shrink malignant tumors in patients by administering bacterial toxins capable of activating immune responses that resulted in tumor hemorrhagic necrosis. In 1975 TNF was identified as the basic protein responsible for this necrotic process. Despite these original encouraging findings, direct administration of large amounts of TNF proved to not only be toxic to the tumor, but to the patient as well, and efforts to leverage TNF as an anticancer drug languished.

Despite this drawback, investigations on the functions of this pleiotropic cytokine in health and disease continued intensely in the coming decades. TNF was demonstrated to be a key regulator of the inflammatory response and for protection against bacterial infection, while its deregulation was shown to lead to diseases such as rheumatoid arthritis, inflammatory bowel disease, septic shock and others. A Greek laboratory under the supervision and guidance of biologist Dr. George Kollias played a central role in identifying and characterizing TNF-mediated disease pathways in animal models of chronic inflammation and autoimmunity. A decisive contribution was made by the laboratory in 1991 when they first provided in vivo, proof of principle, on deregulated TNF production being causal to the development of chronic polyarthritis in transgenic mice, and for showing originally that antibodies against TNF could treat the modeled disease. Today, these treatments constitute highly successful therapies for human patients with rheumatoid arthritis, spondyloarthritides, inflammatory bowel diseases and others.

Recently and in continuation of these investigations, Dr. Kollias' laboratory at the Biomedical Sciences Research Center "Alexander Fleming", in collaboration with Ghent University in Belgium and Fleming's spin-off company Biomedcode Hellas AE, revealed a novel approach for combating systemic toxicity of TNF without reducing its antitumor action. In a study published today in the high impact *Journal of Clinical Investigation*, scientists investigated the cellular mechanisms that are responsible for the systemic toxicity induced by TNF and discovered that these differ from the mechanisms leading to tumor necrosis. The major difference identified was in the differential sensitivity of the two aforementioned mechanisms against TNF when the levels of the major TNF receptor (p55TNFR) are reduced. This reduction in receptor levels appears to prevent TNF systemic toxicity, while still permitting effective tumor necrosis. Taking advantage of these findings, the scientists succeeded in treating melanoma tumors in mice by administering TNF and simultaneously decreasing TNF receptor levels (genetically or through the use of antibodies). With this approach, the researchers managed to treat the tumor without toxic side-effects for the organism.

These novel findings will need to be further tested in other mouse models of cancer before attempting to translate them into applications in the clinic. The researchers hope that their findings will provide a framework for the development of an innovative model of personalised medicine, consisting of determining TNF receptor (p55TNFR) levels in patients before administering tailor-made doses of TNF against tumors. This type of approach is expected to result in safer and more effective TNF-based therapeutic interventions for cancer and other diseases.

Related publication

Van Hauwermeiren F., Armaka M., Karagianni N., Kranidioti K., Vandenbroucke R.E., Loges S., Van Roy M., Staelens J., Puimège L., Palagani A., Vanden Berghe W., Victoratos P., Carmeliet P., Libert C., Kollias G. 2013. Safe TNF-based antitumor therapy following p55TNFR reduction in intestinal epithelium. J Clin Invest. doi:10.1172/JCI65624.

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Information

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