Institute of Molecular Biology and Biotechnology Foundation for Research and Technology-Hellas

PRESS RELEASE

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IMBB researchers reveal a novel mechanism of long non-coding RNAs in the regulation of mammalian immune responses

Research carried out at the Institute of Molecular Biology and Biotechnology, the results of which were published in the international scientific journal "*Proceedings of the National Academy of Sciences of the United States of America"*, revealed new mechanisms of gene mobility and transcriptional activation in the eukaryotic cell nucleus of immune cells.

In diploid organisms, such as humans and mice, trans-allelic interactions control gene expression, providing a tight spatial and temporal level of transcription regulation. Although homologous trans-allelic interactions are quite abundant in various organisms such as Drosophila, plants, and fungi, they have not been widely reported in mammals. All these trans-sensing regulatory mechanisms ultimately point to the complex regulation of physiological processes in a cell. Innate immune responses, although tightly regulated, lack such mechanistic insight regarding the dynamic regulation of chromatin and genome organization.

Macrophages, as crucial mediators of an innate immune response, can be activated by lipopolysaccharide (LPS) of Gram-negative bacteria via Toll-like receptor 4 that ultimately leads to the activation of several classes or responsive genes, such as the cytokine tumor necrosis factor alpha (TNFα). TNFα is a proinflammatory cytokine with a critical role in the initiation of innate and adaptive immune responses. Although TNFα deficiency causes increased susceptibility to infection, resulting in complete lack of B-cell follicles or causing tuberculosis, prolonged high concentrations of TNFα can result in severe tissue damage, autoimmunity, and cancer. It is evident that a tightly regulated balance of TNFα levels is of critical importance. Tnfα gene transcription is controlled in a cell type-specific and stimulus-specific manner. Nonetheless, it also requires a tight spatial and temporal level of regulation.

The results of the research group, headed by the Assistant Professor Babis Spilianakis, indicate that biallelic expression of TNFα alleles requires their homologous pairing which is regulated by the expression of long non-coding RNAs as well as other proteins including an enzyme overexpressed in tumors in order to regulate food uptake.

Investigation of the mechanisms involved in the induction and maintenance of TNFα maximal levels is of great importance for both basic research and clinical practice. First, because a mechanism controlling somatic homologous pairing and allelic expression may be occurring in a wide range of inducible systems, and second, because the identification of ways to exploit such a mechanism could be used in the future to study and possibly resolve the deregulation of gene expression in disease models.

For more information please contact:
Prof. Charalampos G. Spilianakis
Webpage: www.SpilianakisLab.gr
Tel.: 2810-391163
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