Epigenetic alterations: the key for cancer immunology?

Epigenetic alterations in cells play a part in the development of cancer. **Dr Vaios Karanikas** and **Prof Anastasios Germenis**, of the Immunoepigenetics project, explain their team's innovative approach to cancer immunology, with a view to forming a better understanding of carcinogenetic mechanisms and to improve cancer immunotherapy

Research scientist in the laboratory working on the Immunoepigenetics project

The Immunoepigenetics project

(Anti-tumour CD8 immunity Influenced by Epigenetic alterations) is working towards the goal of cancer immunology. The hypothesis of the project is that the spreading of epigenetic alterations within cancerous cells is also affecting the expression of immune genes, and/or other genes of immune cells. This in turn, is then altering the ability of the immune system to combat tumours – a key element in carcinogenesis. This theory has been postulated before, however. So why is the work being done on the project igniting the scientific community to such a degree? Dr Vaios Karanikas and Prof Anastasios Germenis believe it is down to the novel approach taken by the Immunoepigenetics team. "This study approaches the epigenetics of the immune system of cancer patients through their functional consequences on the effector CD8 T cell anti-tumour immune response. Moreover, since one of the tools used for these studies are epigenetic drugs, this project offers a unique methodological approach for screening the efficacy of these on the immune functions, prior to therapeutic applications. This innovative approach for cancer immunology creates a fertile common ground upon which the forefront field of genetics, along with cellular immunology, can work towards the better understanding of carcinogenetic mechanisms and the improvement of cancer immunotherapy."

Researching the nature of cancer

Epigenesis characterises the process of change that is not itself genetic – it is the external influences exerted upon an

entity, such as genes or cells. Cancer is an epigenetic disease in which external influences (alterations) cause cellular gene hypermethylation (the addition of a methyl group to DNA which causes a reduction of gene expression and protein production) and global hypomethylation (a decrease in epigenetic methylation in DNA). Crucially this hypermethylation and the resulting silencing of tumour suppressor genes is a major carcinogenic factor, whilst the significance of DNA methylation and epigenetic aberrations, remains to be elucidated. "Emerging large-scale research efforts, question whether the epigenetic alterations in cancer have a germline or somatic origin as well as if these damages are the cause or the result of the disease. Further, all efforts thus far attempting to answer these and many other practical questions – including the therapeutic potential of epigenetic drugs – have focused on the epigenetic study of tumour-related genes only in cancer cells," notes Karanikas. "However, what I would say is that it is not unreasonable to assume that for the same reasons and/or of the same origin, similar alterations occur concomitantly in other genes and in cells other than cancer cells."

The hope of Immunotherapy

This hypothesis – that a 'spreading' of epigenetic alterations is taking place in not just genes of cancerous cells but also in genes of immune cells – which underlies the project, is the reason why it is causing such a stir. It is literally taking the growing field of cancer immunology to an unprecedented level. Karanikas and Germenis elaborate, "Immunotherapy is regarded as a rather promising alternative for cancer treatment, with large investments by European scientific and commercial sectors. Nevertheless, the current status of this field is at a stand-still, desperately needing clarification of the mechanisms responsible for the limited tumour regressions achieved (about five per cent), signifying the existence of unresolved aspects of current approaches."

Indeed, this increase of research in immunotherapy has lead to a plethora of results and findings, bolstering knowledge of cancer immunology. However, despite that in this research cellular immune responses against tumours were characterised in depth, cancer immunotherapeutic approaches have not achieved clinically effective results. In addition, the involvement of epigenetic mechanisms in the ontogeny of the immune system is well documented, albeit very little is currently known concerning the epigenetic damages possibly affecting immune genes throughout their lifespan. At the same time, the study of tumour cells and tumour-related genes has resulted in the identification of a wide collection of epigenetic alterations of unknown origin.

Any epigenetic aberration of immune genes will affect anti-tumour immune responses, and if this aberration occurs on the CD8 T cell, then the ability of the immune system to combat tumours is severely compromised

This research has been the launch pad for Immunoepigenetics, with the team using it to focus their efforts into a key areas. The team postulate that any epigenetic aberration of immune genes will affect anti-tumour immune responses, and if this aberration occurs on the CD8 T cell, then the ability of the immune system to combat tumours is severely compromised. These effects, it is noted, are expected due to the 'hurricane' nature of cancer. Karanikas states that it's "astonishing why epigenetic alterations of genes (immune or otherwise) in immune cells have never been studied in cancer. The research at Immunoepigenetics comes at a timely juncture to address one of the most challenging aspects of current approaches to effective anti-cancer immunotherapy and potential positive findings are certain to cause a revision of basic ideas and principles – not only for immunosurveillance and carcinogenesis itself – but also for the treatment of cancer using immunotherapy." ★

At a glance

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Anti-tumour CD8 immunity Influenced by Epigenetic alterations: IMMUNOEPIGENETICS

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Contact Details:
Dr Vaios Karanikas, PhD
Scientific Co-ordinator, Cancer Immunology Unit
Department of Immunology & Histocompatibility
School of Medicine
University of Thessaly, GR- 411 10 Larissa, Greece
T: +30 2410 685718
F: +30 2410 685549
E: vkaran@med.uth.gr

Prof Anastasios E Germenis, MD, PhD
Chairman, Department of Immunology & Histocompatibility
School of Medicine, University of Thessaly
T: +30 2410 685718
F: +30 2410-685549
E: agermen@med.uth.gr

Anastasios Germenis (left)
Vaios Karanikas (right)

Vaios Karanikas, Scientific Coordinator

Dr Karanikas, graduated in Immunology and received his PhD in Australia. Three years ago he returned to Greece establishing the cancer immunology unit; leading a dynamic team of young scientists with an aim to dissect the nature of the immunological response in cancer and understand how effective anti-tumour immunity can be generated.