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BRUSSELS BRANCH

OF HUMAN CANCER CELL GENETICS

BRUSSELS, BELGIUM

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BRANCH DIRECTOR'S REPORT

The Brussels Branch specializes in cancer immunology and cancer genetics. The notion that the immune system might be enlisted to rid the body of cancer draws on past work at the Branch which revealed that most human tumors bear antigens that can be recognized by cytotoxic T lymphocytes (CTLs). Some of these antigens are highly tumor-specific, whilst others are expressed on certain normal cells. A number of antigens have been found on many different types of tumors, suggesting that a therapeutic strategy targeting such antigens could be used to treat a wide range of cancers. The Brussels Branch continues the search for tumor antigens, and evaluates their therapeutic potential in vaccine trials of cancer patients.

T. Boon

RESEARCH REPORT

CYTOKINE GROUP

Led by Dr. Jean-Christophe Renauld, the group studies the biology of interleukin (IL) -9 and IL-22, two cytokines discovered at the LICR Brussels Branch. IL-9 is a TH2 cytokine that plays a role in immune responses against intestinal parasites, and asthma. IL-22, originally identified as a gene induced by IL-9 in T lymphocytes, upregulates the production of acute phase reagents in liver. Its activity in inflammatory responses is modulated by a specific antagonist; the IL-22 binding protein. The role of IL-9 and IL-22 in inflammation is currently investigated using transgenic and gene-targeted mice for these cytokines and their receptors.

First, IL-9 transgenic mice, which have a high level of this cytokine in all tissues, are characterized by a high susceptibility to the development of T cell lymphomas. Another major aspect of IL-9 biology is its effect on the growth and differentiation of mast cells. IL-9 transgenic mice show increased numbers of mast cells in the gut and airways. Finally, a puzzling activity of IL-9 is a selective increase in the peritoneal B1b cell subpopulation. Although the specificity of these cells is far from clear, they might be related to some auto-immune processes. In line with the oncogenic activity of IL-9 in transgenic mice, this cytokine was shown to be a potent anti-apoptotic factor for T cell lymphomas. The anti-apoptotic effect of IL-9 does not involve MAP-kinases but is mediated by the Janus tyrosine kinase (JAK)/Signal transducers and activators of transcription (STAT) pathway. Therefore, the group is now focusing on the characterization of genes whose expression is regulated by IL-9 through the activation of STAT transcription factors.

HUMAN TUMOR ANTIGEN GROUP*

The group led by Dr. Pierre van der Bruggen is defining antigenic peptides encoded by genes like those of the MAGE family, which are expressed by cells from many different cancer types. Therapeutic vaccination of cancer patients with MAGE peptides is now in progress. The identification of additional antigenic peptides is important to increase the number and type of patients eligible for therapy, and to provide tools for a reliable monitoring of the immune response. Stimulation of $CD8^+$ T lymphocytes with antigen-presenting dendritic cells infected with viruses carrying MAGE genes has led to the identification of a large number of new antigenic peptides presented by HLA class I molecules. Similarly, stimulation of $CD4^+$ T cells with dendritic cells pulsed with a MAGE protein has revealed new antigenic peptides presented by HLA class II molecules. The finding that almost every cancer patient whose tumor expresses a MAGE gene has at least one HLA molecule presenting a MAGE antigenic peptide suggests numerous possibilities for therapeutic vaccination. Reliable methods to monitor the $CD4^+$ T cell response to cancer vaccines are in development.

The group is also involved in the study of functional defects of T cells. We have observed that human cytotoxic T lymphocytes (CTL) clones lose their specific cytolytic activity and cytokine production under certain stimulation conditions. These inactive CTL simultaneously lose their labeling by an HLA-peptide tetramer, even though the amount of TCR-CD3 at their surface is not reduced. Our results suggest the existence of a new type of functional defect of CTL.

* Clinical Trials Program participant

IMMUNOGENETICS MONITORING GROUP*

Dr. Aline Van Pel's group collaborates with the group of Dr. Pierre Coulie at the Institute for Cellular Pathology (Catholic University of Louvain, Brussels) to elucidate whether or not a correlation between the clinical responses and the anti-vaccine T cell responses exists in the minority of patients who display tumor regression after MAGE vaccination. A very sensitive method of CTL detection was set up last year, involving *in vitro* stimulation of blood lymphocytes, tetramer analysis, obtention of CTL clones, and analysis of their TCR sequences. This approach was used for 12 patients who showed tumor regression after vaccination with a MAGE-3 peptide presented by HLA-A1. The vaccines contained either peptides alone, or a recombinant ALVAC canarypox virus, produced by Aventis. An anti-MAGE-3.A1 CTL response was found in seven patients. All the CTL responses were monoclonal. Among 16 vaccinated patients who did not display tumor regression, only two had an anti-MAGE-3.A1 CTL response. In collaboration with the group of Dr. G. Schuler (Erlangen, Germany), CTL responses were analyzed in melanoma patients vaccinated with mature dendritic cells pulsed with the MAGE-3.A1 peptide. CTL responses were found in three patients showing tumor regression. In each of these responses, several CTL clones were amplified, a polyclonality that contrasts with the monoclonal responses observed in patients vaccinated with peptide or ALVAC. One patient who did not respond clinically to vaccination with dendritic cells was analyzed, and no MAGE-3.A1 CTL could be found. These results suggest that the occurrence of a detectable CTL response shows some degree of correlation with tumor regression, opening the possibility that a limiting factor for the anti-tumor effect of MAGE vaccination is the intensity of the CTL response to the vaccine antigen.

TUMOR GENETICS GROUP

Human tumors express specific antigens arising from the activation of genes, such as *MAGE*, *BAGE*, *GAGE* and *LAGE/NY-ESO1*, which are expressed only in tumors and normal germ cells, and are known as "cancer/testis" (CT) antigens. As germ cells are not subject to scrutiny by the immune system, CT antigens encoded by these genes are strictly tumor-specific. The group of Drs. Etienne De Plaen and Charles De Smet is trying to identify new genes that are specifically expressed in tumors and germ cells. Screening procedures based on differential expression profiling have isolated several genes with cancer and germline specific expression. Most of these genes are normally expressed in spermatogonia, the pre-meiotic stage of sperm development, and are located on the X chromosome. Efforts are underway to determining the function of these "cancer-testis" (CT) genes. To analyze the functions of a MAGE protein, MAGE-A1, Dr. Etienne De Plaen and his group used yeast two-hybrid screening, and found an interaction between MAGE-A1 and the transcriptional regulator SKIP. SKIP is an adaptor protein that connects DNA-binding proteins to proteins that activate or repress transcription. The results suggest that by binding to SKIP and recruiting histone deacetylase 1, MAGE-A1 protein represses transcription. The group is now trying to identify the genes that are regulated by MAGE-1 by using an inducible transfected *MAGE-A1* gene and microarray technology.

Finally, the group is also studying the mechanisms leading to the activation of CT genes in tumors. The group has previously shown that DNA methylation is an essential component of their repression in normal somatic tissues. The promoters of these genes contain a high density of CpG islands, but unlike classical CpG-rich promoters they are heavily methylated in all somatic tissues. In contrast, the promoters are unmethylated in germ cells, and in tumors that express these genes. Demethylation and therefore activation of CT genes in tumors was found to be coincident with overall genome demethylation, a process known to occur in many cancers. The group is currently studying the mechanisms of demethylation of these genes in tumors. Activation of CT genes in tumors appears to rely on a historical

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event of demethylation, and on the presence of specific transcription factors that maintain the promoter region in an unmethylated state.

TUMOR IMMUNOLOGY GROUP

The central research theme of Dr. Benoît Van den Eynde's group is the study of tumor antigens recognized by T lymphocytes for cancer vaccines in human patients. As well as a continued effort to identify additional antigens of interest, the group also addresses a number of fundamental or mechanistic issues that have a direct impact on the utilization of such antigens. The antigens consist of peptides, presented by MHC molecules at the cell surface, which derive from intracellular proteins degraded by the proteasome. The intracellular pathway leading from the antigenic protein to the peptide/MHC complex is known as "antigen processing". The group is currently studying the processing of several human tumor antigens by the proteasome, and is particularly interested in the processing differences observed between the standard proteasome, which is present in most cells, and the immunoproteasome which is found in some dendritic cells and in cells exposed to interferon-gamma.

The group is also studying a mouse preclinical model of cancer immunotherapy, to define the optimal conditions to induce effective anti-tumor responses by various vaccination approaches against particular antigens. This has uncovered a powerful mechanism of tumor resistance which is based on tryptophan catabolism by indoleamine-2,3 dioxygenase, an enzyme frequently expressed in tumors. The resulting local tryptophan shortage appears to prevent the proliferation of lymphocytes at the tumor site. Inhibitors of indoleamine-2,3 dioxygenase are currently being tested *in vivo* for their ability to counteract this tumor resistance mechanism. To obtain the most relevant information from such preclinical models, the group is attempting to generate a new mouse melanoma model in which tumors expressing a given antigen can be induced using a transgenic system based on Cre-lox recombination. This should recapitulate the long-term host/tumor relationship that occurs in humans when a tumor slowly develops within a normal tissue.

THERAPEUTIC VACCINATION GROUP*

Because of their tumor specificity, MAGE antigens are promising candidates for cancer vaccine development. The group led by Drs. Marie Marchand and Nicolas Van Baren, designs and carries out such clinical trials. Trials investigating either MAGE peptides or recombinant MAGE proteins, and a recombinant ALVAC virus encoding a MAGE minigene have been completed or are ongoing. All of these cancer vaccines are very well tolerated by the patients. Tumor regressions have been observed in approximately 20% of the vaccinated patients with metastatic melanoma, with complete or partial clinical responses being observed in approximately 10% of patients.

While it is possible to make CTL recognize and kill autologous tumor cells *in vitro*, the precise way to induce an effective CTL response against a MAGE antigen in cancer patients is not yet known. Clinical vaccination trials have two main objectives. First, the effectiveness of various vaccination modalities can be assessed by following the clinical evolution of the tumor, by analyzing whether a specific CTL response to the vaccine antigen occurred, and by determining whether immunological and clinical responses are correlated. Secondly, T lymphocytes and tumor samples collected at different time points during vaccination can be analyzed in detail, improving our understanding of what happens in patients who experience regression of metastatic lesions, and perhaps explaining why this does not happen in the majority of patients with overall disease progression. This knowledge can then be used to design new vaccination modalities.

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SIGNAL TRANSDUCTION GROUP

The group of Dr. Stefan Constantinescu joined the LICR in 2001, and reinforced and extended the focus on signal transduction mechanisms involving cytokine receptors. Cytokines and their receptors are critical for the formation of mature blood cells and for the function of the immune system. Signaling by cytokine receptors is triggered by ligand-induced changes in receptor dimerization/oligomerization, which induces the activation of cytosolic JAK proteins. Activated JAK proteins phosphorylate downstream STAT proteins, which dimerize in the cytosol and are translocated to the nucleus where they bind to specific promoter sequences and regulate transcription. The group studies the signal transduction mechanisms and biological functions of cytokine receptors such as the receptors for erythropoietin, thrombopoietin, IL-2 and IL-9. The assembly of cell-surface receptor complexes, the structure and orientation of the transmembrane and cytosolic juxtamembrane domains, and the regulation by JAK kinases of receptor traffic are major focuses. The group also studies the mechanisms by which STAT proteins become constitutively activated and how they function in transformed hematopoietic or patient-derived leukemia cells.

PUBLICATIONS

PRIMARY RESEARCH ARTICLES

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REVIEWS/ COMMENTARIES/BOOK CHAPTERS

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