LUDWIG INSTITUTE FOR CANCER RESEARCH

Brussels Branch
of Human Cancer Cell Genetics

Brussels, Belgium

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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, while 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.

The Brussels Branch is also involved in research on the immunological functions of several cytokines, particularly IL-9 and IL-22 which have been discovered at the Branch. The signaling pathways and genes induced by these cytokines are also studied.

Thierry Boon

Research Report

Therapeutic Vaccination Group

Because of their tumor specificity, MAGE antigens are promising candidates for cancer vaccine development. The Group, led by Marie Marchand and Nicolas Van Baren, designs and conducts clinical trials investigating either MAGE peptides, recombinant MAGE proteins, or a recombinant ALVAC virus encoding a *MAGE* minigene. All these cancer vaccines are very well tolerated by the patients. Tumor regressions are observed in 10 to 20% of the vaccinated patients with metastatic melanoma, with complete or partial clinical responses being observed in 5 to 10% of the patients.

While it is possible to derive CTL that recognize and kill autologous tumor cells *in vitro*, the 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. The first objective is to assess the effectiveness of various vaccination modalities; 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. The second objective is to analyze T lymphocytes and tumor samples collected at different time points during vaccination to better understand what happens in patients who experience regression of metastatic lesions, and why this does not happen in the majority of patients with overall disease progression. This knowledge will be used to design new vaccination modalities.

Immunotherapy Analysis Group

The Group led by Drs. Aline Van Pel and Danièle Godelaine, in collaboration with Drs. Pierre Coulie (Institute of Cellular Pathlogy, Université Catholique de Louvain, Belgium) and Kris Thielemans (Vrije Universiteit Brussel, Belgium) is pursuing vaccination of melanoma cancer patients with tumor-specific MAGE-3.A1 antigen as peptide alone, as recombinant ALVAC canarypox, or with autologous dendritic cells pulsed with the antigenic peptide. The immune response of each vaccination approach, joined to a possible correlation with clinical outcome, has remained the main research interest. The Group has already described how the well established HLA-peptide tetramer approach allowed the follow up of the MAGE-3.A1 anti-vaccine CTL response, through the isolation of CTL clones and the genetic analysis of T cell receptor (TCR) sequences. For some of these patients, tumor cell lines were established from tumor samples removed by surgery. From these metastases, tumor infiltrating lymphocytes were also isolated and cloned. These anti-tumor CTL clones were found to be directed against epitopes unrelated to the vaccine, such as mutated or differentiation antigens. In one patient, a strong immune reactivity against epitopes of the MAGE-C2 protein expressed by the tumor was found. Following the characterization of their TCR, a genetic analysis has demonstrated the amplification of some of the CTL clones, seen not only in the metastases but also in the blood. Some of these CTL clones were highly enriched in tumor samples relative to the blood. Such expansion of several anti-tumor CTL clones, including some directed against MAGE-C2 epitopes, was confirmed in another clinically responding patient after vaccination with MAGE-3.A1 antigen. Future research will focus on the understanding of this phenomenon by analyzing other patients including clinical non-responders.

Human Tumor Antigen Group

The Group, led by Dr. Pierre van der Bruggen, is defining antigenic peptides encoded by "cancer-testis" (CT) 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, and the identification of additional antigenic peptides is important to increase the range 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. Efforts are currently devoted to set up assays that accurately monitor CD4+ T cell responses to cancer vaccines. The Group recently validated the use of the first HLA-DP4 tetramer, which was folded with a MAGE-3 peptide for patients vaccinated with peptides. The Group has also validated a quantitative approach to isolate anti-vaccine T cells directed against all possible HLA-peptide combinations that could be targeted by the response for patients vaccinated with a protein.

Functional defects of T cells are also being studied, with the observation that human 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, although the amount of TCR-CD3 at their surface is not reduced. These results suggest the existence of a new type of functional defect of CTL.

Tumor Immunology and Antigen Processing Group

Building on the molecular definition of tumor antigens recognized by T cells, the Group of Dr. Benoît Van den Eynde mainly focuses on two aspects of tumor immunology; the processing of tumor antigens and the study of animal models to optimize cancer immunotherapy and evaluate tumor resistance mechanisms. The Group also recently described several new tumor antigens, which are encoded by cancer-germline gene *MAGE-C2* or derived from melanocytic protein gp100.

Tumor antigens recognized by CTL consist of peptides that are presented by major histocompatibility complex (MHC) molecules at the cell surface and derive from intracellular proteins that are degraded by the proteasome. The intracellular pathway leading from the protein to the peptide/MHC complex is known as "antigen processing". The Group recently described a new mode of production of antigenic peptides by the proteasome, based on that apparatus cutting and pasting peptide fragments to form a new spliced peptide. The first example was a peptide derived from human melanocyte protein gp100. This antigenic peptide is nine amino acids long and is produced by the splicing of two fragments that were initially non-contiguous in the parental protein. The splicing made by the proteasome is tightly coupled to the proteolytic reaction, and appears to occur by transpeptidation involving an acyl-enzyme intermediate. The Group is currently working on a second example of spliced peptide, where the two fragments are rearranged before splicing. The processing differences between the standard proteasome, which is present in most cells, and the immunoproteasome, which is found in dendritic cells and in cells exposed to interferon-gamma, are also being studied. Several tumor antigens were found to be processed differently by the two proteasome types, usually because of a preferential cleavage made by one or the other proteasome within the antigenic peptide itself.

Translation of knowledge about tumor antigens into efficient cancer immunotherapy requires additional studies on the various strategies that can be used. Some of these studies can be performed in preclinical animal models. The currently available murine models are limited by the fact they are based on transplantation of tumor cells, grown *in vitro*, into a healthy animal. This does not recapitulate the long-term host/tumor relationship that occurs in humans when a tumor slowly develops within a normal tissue. To circumvent this limitation and obtain more relevant information from such preclinical models, the Group has designed 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 involves a transgenic mouse strain with an inducible expression of ras and an inducible inactivation of the tumor-suppressor genes of the INK4A locus. The induction is based on recombinase Cre-ER, which is under the control of the tyrosinase promoter. Thus, after topical treatment with tamoxifen, CreER will recombine the transgenes in melanocytes, thereby inactivating INK4A and activating ras. In addition, the induced melanomas will express the model tumor antigen encoded by gene *P1A*, which is also activated by recombination of the transgene. The results show that about 33% of the treated mice develop cutaneous melanomas expressing P1A. These tumors grow slowly and progressively, without causing distant metastases. This model should prove useful to optimize immunotherapy.

Tumor Genetics Group

Human tumors express specific CT antigens arising from the activation of genes, such as *MAGE, BAGE, GAGE* and *LAGE/NY-ESO1*, which are normally expressed only in germ cells. As germ cells are not subject to scrutiny by the immune system, 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 specifically expressed in tumors and germ cells. Screening procedures based on differential expression profiling allowed the isolation of several genes with cancer and germline specific expression. Most of these genes are typically expressed in spermatogonia, the pre-meiotic stage of sperm development, and are located on the X chromosome

Additionally, efforts are also devoted to determining the function of CT genes. To analyze the functions of a MAGE protein, MAGE-A1, Dr. Etienne De Plaen and his team are searching for binding partners of this protein. An interaction between MAGE-A1 and transcriptional regulator SKIP was discovered using yeast two-hybrid screening. 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, the MAGE-A1 protein present in the nucleus represses transcription. The Group is now trying to identify the genes that are regulated by MAGE-A1 by using an inducible transfected *MAGE-A1* gene and the microarray technology.

Dr. Charles De Smet and his team are studying the mechanisms leading to the activation of CT genes in tumors. The Group has previously shown that these genes rely primarily on DNA methylation for their repression in normal somatic tissues, and that their activation in tumors is a consequence of the overall genome demethylation process that often accompanies tumorigenesis. The Group is now focusing on the mechanisms of demethylation of these genes in tumors. Stable activation of CT genes in tumors does not require a permanent demethylating activity, but depends on the presence of specific transcription factors that maintain the promoter region unmethylated. Antisense-mediated knock-down experiments indicated that DNMT1 is the primary DNA methyltransferase maintaining methylation of cancer-germline genes. Transient down-regulation of DNMT1 induced stable activation of cancer-germline genes, supporting the view that hypomethylation of these genes in tumors results from a historical event of demethylation.

Finally, the Group is investigating the gene expression profile of tumor samples and tumor cell lines obtained from melanoma patients who received experimental cancer vaccines. Using microarray and quantitative RT-PCR, the group is trying to identify genes involved in the resistance of tumors to CTL.

Cytokine Group

Led by Dr. Jean-Christophe Renauld, the Group studies the biology of interleukin-9 (IL-9) and IL-22, two cytokines discovered at the 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 being investigated using transgenic and gene-targeted mice for these cytokines and their receptors.

First, IL-9 transgenic mice, that 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 JAK/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.

A study of cytokine function based on auto-vaccination of mice with mouse cytokines linked to non-self proteins or helper peptides was initiated several years ago using IL-9. It has now been extended to IL-12, whose excessive production has been linked to several auto-immune diseases. Auto-vaccination against IL-12 was found to completely protect against some forms of murine experimental auto-immune encephalomyelitis at the expense of reduced resistance against an intracellular parasite such as *Leishmania major*.

Coupling of human IL-9 to a carrier protein was also instrumental in the development of anti-human IL-9 monoclonal antibodies with potent inhibitory activity. These antibodies allowed the first detection of human IL-9 protein production by peripheral blood mononuclear cells (PBMC) stimulated with allergen or helminthic infection. A systematic screening of human plasma samples showed that, while no IL-9 could be detected in sera from normal individuals, it was found in approximately 40 % of patients with Hodgkin's Disease and correlated with nodular sclerosis subtype and negative prognostic factors.

Signal Transduction Group

The Group, led by Dr. Stefan Constantinescu, studies: the mechanisms by which Janus kinases (JAKs) act as chaperones for cytokine receptor traffic; the structure and function of cytokine receptors; and JAK-STAT signaling in blood formation and oncogenesis. During 2004, the Group focused on the structure and function of the thrombopoietin (TpoR) and erythropoietin receptors (EpoR) and their involvement in myeloproliferative syndromes. An extended cysteine scanning mutagenesis of the EpoR juxtamembrane extracellular (JM) and transmembrane (TM) regions led to the isolation of three novel constitutively active EpoR mutants and to the identification of a helix cap structure at the junction between the JM and TM regions. This sequence may become a target for screening of small molecule activators/ inhibitors of the EpoR.

A novel approach was established to study signaling by distinct dimeric conformations of cytokine receptors. Fusion proteins were engineered between a dimeric coiled-coil and the TM and cytoplasmic domains of cytokine receptors in such a way that all seven possible relative orientations of the dimeric receptors were imposed. Using this approach, several active dimeric conformations of the TpoR were identified. As a function of the dimeric conformation, the TpoR appears to activate distinct signaling pathways at different stages of hematopoietic development. The Group is now attempting to ascribe the signaling molecules responsible for this differential signaling. The mechanisms by which STAT proteins become constitutively activated and how they function in the nucleus of transformed hematopoietic or patient-derived leukemia cells are also being studied.

In collaboration with the laboratory of Dr. William Vainchenker (Institut Gustave Roussy, Villejuif), the Group has contributed to the discovery of a point mutation of the pseudokinase domain of JAK2, which is present in a majority of Polycythemia Vera patients and in patients with essential thrombocythemia and idiopathic myelofibrosis. Signaling downstream of this JAK2 mutant and its effects on cytokine receptor traffic and erythroid/myeloid differentiation are major focuses.

Publications

Primary Research Articles

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Reviews / Commentaries / Book Chapters

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