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Editorial overview

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Cornelis J.M. Melief is a professor of immunology at Leiden University Medical Center and Chief Scientific Officer of the company Immune System Activation (ISA), also based in Leiden. He is interested in the development of therapeutic vaccines against cancers of viral and non-viral origin. His current focus is on immunotherapy of HPV16-induced cancers and on local delivery of therapeutic monoclonal antibodies.

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Olivera J. Finn, Ph.D. is a Distinguished Professor of Immunology and Chair of the Department of Immunology at the University of Pittsburgh School of Medicine and Co-Leader of the Cancer Immunology Program of the University of Pittsburgh Cancer Institute. She is interested in developing vaccines for cancer prevention and to that end she has been working on identifying antigens abnormally expressed on premalignant lesions and cancer stem cells.

While adaptive immune defense against virally induced cancers has been widely accepted for a long time, immunosurveillance of cancers of non-viral origin has been hotly contested. In fact 'inflammation' has been linked to cancer promotion rather than protection, as demonstrated by the increased incidence of colorectal cancer in patients with Crohn's disease or ulcerative colitis. Recent evidence, however, shows that immunosurveillance by adaptive immunity also operates in non-viral cancers such as colorectal cancer and melanoma, and its presence and anti-tumor effects are distinguishable from other types of inflammation that determine the pro-tumor microenvironment. Most importantly, a distinction can now be made between 'bad' inflammation, characterized by high levels of STAT3 transcription factor activity and infiltration of cancers by Th2 cells, Foxp3-positive regulatory T cells, myeloid-derived suppressor cells (MDSC) and M2 macrophages, and 'good' inflammation, characterized by infiltration with Th1 cells and CD8+ cytotoxic T lymphocytes (CTL), M1 macrophages and ample numbers of dendritic cells (DC) capable of cross-presenting tumor-associated antigens. Individual cancer types, traditionally identified as a single histological type, such as colorectal cancer (CRC) or malignant melanoma, turn out to be extremely heterogeneous with regard to such immune parameters with profound implications regarding prognosis and options for immunotherapy. A decisive function in creating the distinct 'good' or 'bad' leukocyte infiltrates appears to be exerted by the chemokines produced within the tumor. Distinct chemokine expressions are related to attracting tumor-promoting leukocytes, whereas others are linked to the attraction of leukocytes promoting tumor regression or failure to metastasize. The great challenge is now to establish which oncogenic cell-transforming events that lie at the basis of the malignant transformation are responsible for the expression of distinct STAT transcription factors, associated chemokine expressions and the resulting attraction of 'good' or 'bad' leukocytes. Obviously many other aspects of the tumor microenvironment dictate the impact of the innate and adaptive immune responses on the individual tumor's behaviour.

In this issue we have brought together a series of authoritative reviews from experts in immunity against virus-induced cancers as well as non-viral cancers, to address the issues of 'good' and 'bad' inflammation and ways to modulate tumor microenvironment in favor of 'good' inflammation.

Of the five viruses known to cause cancer, Hepatitis B virus (HBV), Hepatitis C virus (HCV), high risk Human Papilloma virus (HPV), Epstein Barr virus (EBV) and Merkel sarcoma polyoma virus, preventive vaccines now exist for HBV and two high risk HPV types (HPV16 and18).

2 Tumour immunology

The development of these vaccines is a great success story in the prevention of cancer and these achievements are dealt with in the reviews of Ding-Shinn Chen and colleagues and Richard Roden and colleagues. Remaining issues in preventive HBV vaccination are breakthrough infections and worldwide delivery of the vaccine to all populations that need it. The latter issue also applies to preventive HPV vaccination. In addition, the current preventive HPV vaccines protect against about 75% of all cervical cancer, the remaining 25% being caused by high risk HPV types other than HPV16 and 18. In their review Roden and colleagues discuss alternatives to L1 VLP vaccination. One particularly attractive strategy is to vaccinate with a linear N-terminal highly conserved sequence of the viral capsid L2 protein. If offered to the immune system in a properly immunogenic context, neutralizing antibodies to this B cell epitope-containing region are elicited that have broadly neutralizing capacity against a wide range of HPVs. Van der Burg and Melief review the design and implementation of a synthetic long peptide vaccine with therapeutic ability against high risk HPV16 and established lesions induced by this virus, which alone is responsible for half the cases of cervical cancer and most of the cases of vulvar and HPV-positive head and neck cancer. Half of the patients with high grade Vulvar Intraepithelial Neoplasia achieved complete regression of disease when treated with this vaccine and clinical responses were associated with robust T cell immune responses. This strategy lends itself to therapeutic vaccine development against other cancer viruses and against non-viral cancers. Alan Rickinson and colleagues highlight the latest developments in EBV immunobiology. EBV, like other herpes virus family members utilizes a plethora of immune evasion strategies to avoid recognition by both CD8 CTL and CD4 helper cells. Nonetheless T cells control EBV-induced malignancies as demonstrated by both the success of adoptive transfer of EBV-specific T cells in eradicating immunodeficiency-associated EBV + B cell malignancies and the increasing evidence that susceptibility to EBV-induced disease is controlled by HLA polymorphisms. In EBV + Hodgkin's disease, the cancer cells often express the CCL17 and CCL22 chemokines, attracting Th2 and T regulatory cells, thereby avoiding tumoricidal immune responses. Whereas for EBV and HCV no effective preventive vaccines are available, an EBV viral envelope-based vaccine has reduced the risk of contracting infectious mononucleosis without stopping the infection.

Cramer and Finn review the epidemiology of cancer and highlight the reports that acute infectious diseases in childhood protect against many types of cancer later in life, whereas many chronic inflammatory conditions predispose towards the development of cancer. They propose that the mechanism responsible for this modu-

lation of cancer risk is immunosurveillance. Their hypothesis is that immunity or tolerance to many cancer-associated antigens, self molecules that are abnormally expressed in tumors, can be generated during non-cancerous diseases earlier in life that also lead to abnormal expression of these molecules. Hence immunosurveillance of non-viral cancers may in part be due to revival of immune memory installed earlier by immune responses to common antigens abnormally expressed by stressed and diseased tissues other than cancer. Fridman and colleagues review the overwhelming evidence from tissues of a large series of patients that the prognosis of colorectal cancer (CRC) is crucially dictated by the degree of infiltration by cytotoxic T lymphocytes in the tumor center and in the tumor margins. The group has developed this to a practical prognostic assay independent of the standard pathological classification. Their results argue in a powerful way for separate therapeutic approaches to the subgroups of CRC patients identified by this methodology. Whether or not cytotoxic cells or other leukocytes are recruited into the cancerous tissue appears to be determined by the chemokine expression pattern in the tumor. In contrast to cytotoxic T cells, Myeloid Derived Suppressor Cells (MDSC) attracted into tumors are a prognostically unfavorable sign. These cells are the result of abnormal hemopoiesis that is manifest in many cancers and exerts powerful immunosuppressive capacity, in particular towards CD8 + CTL. The review of Bronte and colleagues clarifies the properties of MDSC and discusses the transcription factors that lie at the basis of the emergence of this subpopulation of immature myeloid cells. These results allow more direct approaches to control MDSC proliferation in cancers or mediate their demise once generated. The importance of cancer microenvironment is also reviewed by Gajewski and colleagues, this time for malignant melanoma. Again the message is that melanomas are markedly heterogeneous with respect to gene expression patterns and leukocyte infiltrates. Favorable chemokine expression patterns predict attraction of CD8 + CTL whereas unfavorable patterns predict either absence of CTL's or influx of immunosuppressive leukocytes such as MDSC. Other negative regulators of favorable immunity were expression of IDO or PD-1, influx of FOXP3-positive cells and absence of CD80/CD86 co-stimulatory molecules. Lampen and van Hall review the evidence for MHC class I loss seen in experimental and human cancers. While such loss is prognostically unfavorable, they review the strategy to arouse an alternative repertoire of T cells, specifically directed against cancer cells with antigen processing defects leading to the loss of MHC class I. These T cells are directed against peptides that are presented by classical MHC class I molecules in the absence of competition by TAP-transported peptides. Alternatively such peptides can also be presented by non-classical MHC class I mol-

ecules such as HLA-E when the classical HLA-A and HLA-B molecules are completely lost. Last but not least, Riddell and colleagues discuss adoptive transfer of tumor-specific T cells generated by tumor-specific TCR transduction. They address the importance of the choice of the TCR as well as the transduction technology. They also explore what might be the best recipient

T cell population for TCR transduction and expected *in vivo* efficacy.

Together these contributions provide a comprehensive overview of not only the awesome power of preventive and therapeutic immunological strategies to combat cancer, but also the hurdles that still need to be overcome.