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Review

Scientific contributions toward successful cancer immunotherapy in The Netherlands

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ABSTRACT

This historical overview shows that immunologists and clinicians from The Netherlands have contributed in a major way to better insights in the nature of cancer immunity. This work involved elucidation of the nature of cancer-associated antigens in autologous and allogeneic settings in addition to understanding of the cellular basis of natural immune responses against cancers and of important immune evasion mechanisms. Insight into such basic immunological mechanisms has contributed to the development of innovating therapies.

1. Introduction

Cancer therapy rests traditionally on the three pillars surgery, radiation and chemotherapy. While these are still the basis of current cancer therapy, specific inhibitors of aberrant kinases in cancer cells and immunotherapy with monoclonal antibodies against surface molecules of cancer cells have drastically changed the landscape of cancer therapy, creating opportunities where none existed. Recently, monoclonal antibody therapies were also introduced against target molecules not expressed on the cancer cells themselves, but rather on stromal cells responding to the cancers, notably T cells. The most successful of these are monoclonal antibodies against the so-called checkpoint blocking molecules on the surface of T cells such as CTLA-4 and PD-1. In healthy people, these molecules are involved in T cell homeostasis, preventing overshoot of T cell responses toward inflammation and auto-immunity, but in cancer patients the inhibitory action of these molecules smothers potentially beneficial T cell responses. The last 50 years have witnessed the extraordinary development of a variety of cancer immunotherapies next to the traditional cancer therapies, starting with the observation that cancers are immunogenic and naturally elicit immune responses and with the appreciation that monoclonal antibodies of uncanny specificity, generated in unlimited amounts, can be used for immunotherapy of cancer in a highly reproducible and standardized manner. This review summarizes the main contributions of Dutch immunologists to the field of cancer immunology and immunotherapy. This field has witnessed a transition from the initial perception of tumor immunology and immunotherapy as hardly better than homeopathy to a highly respected branch of mainstream immunology, involving insights into the most intricate pathways of interaction between diseased tissues and the host, thereby permitting the development of sophisticated novel therapies.

2. The early studies

Cancer immunology in The Netherlands started with godfather Philip Rümke, a physician and first head of the department of tumor immunology at the Netherlands Cancer Institute (Nederlands Kanker Instituut, NKI)/Antoni van Leeuwenhoek Huis (founded in 1913) in Amsterdam. Philip did his thesis work on autoantibodies against spermatozoa as a cause of infertility in men and quickly realized that autoimmunity against cancer cells can be of benefit for cancer patients. In 1965 he published that a breast cancer patient with anti-cytoplasmic auto-antibodies survived remarkably longer than the 195 other breast cancer patients and survived not only her surgeon, but also her pathologist and radiotherapist [1]. Later on

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he initiated a clinical trial in patients with metastatic melanoma and investigated the effect of painting some metastases with the contact sensitizer dinitrochlorobenzene (DNCB) followed by dacarbazine chemotherapy. The results, published in 1983 (abstract[1]) and in 1997 [2], showed complete and permanent regressions in some patients with severe allergic reactions in the painted skin metastases as side effect.

Interestingly, a related and more elaborate approach to melanoma therapy was recently pioneered in mice by Rosalie Luiten and colleagues, who showed that effective melanoma therapy is possible by the combined use of the skin depigmenting compound monobenzone, a tyrosinase binder, and the TLR ligands imiquimod and CpG [3]. In 1972, Rümke, together with Jan de Vries, his successor as head of the tumor immunology department at the NKI, published the existence of cytotoxic lymphocytes in the blood of melanoma patients [4]. Two years later they observed cytotoxicity exerted by both T cells and non-T cells on cultured melanoma cells [5]. This actual description of NK cells "avant la lettre" (the non-T cells) preceded the naming of NK cells or K cells by K. Kärre and R. Kiessling from Sweden and Ronald Herberman from the US. Another early pioneer of human NK cells was Reinder Bolhuis [6]. In 1975 auto-antibodies against melanoma cells were detected in the serum of melanoma patients [7]. Jan de Vries and Hergen Spits subsequently pioneered the culture of human T lymphocyte clones against EBV-transformed B cells and against autologous melanoma cells. These results from 1982 and 1984 [8,9] were decisive for later adoptive T cell transfer trials. Perhaps even more importantly, Spits and De Vries were the first to show that antibodies against the CD3 T cell surface antigen can induce T cell-mediated cytotoxicity [10]. This finding established the basis for the later use of bi-specific anti-CD3/anti-tumor antibodies for anti-cancer therapy, an approach that is now a major clinical drug development line in many pharmaceutical companies.

3. Exploitation of immunity to alloantigens for cancer immunotherapy

Another strain of cancer immunology and immunotherapy in The Netherlands originated from the field of allo-immunology, a traditionally strong field in The Netherlands thanks to the pioneering work of Jochem Van Loghem and colleagues on red blood groups. In 1977, Els Goulmy and Jon Van Rood described CTL against the first human counterpart of a minor histocompatibility (minor H) antigen: the male antigen HY, later followed by the discovery of the HA-1 and HA-2 antigens [11–14]. These discoveries paved the way for understanding the difference between the allogeneic T cell-mediated graft versus host (GVH) and graft versus leukemia (GVL) effects, because obviously T cells against minor H antigens with hematopoietic cell specific expression cannot cause GVH after allogeneic stem cell transplantation, since only residual leukemia cells express such antigens, the patient bone marrow having been replaced with minor H negative cells. The validity of these concepts was later conclusively shown by Fred Falkenburg and colleagues who showed that T cells against the hematopoietic-specific HA-1 and HA-2 antigens can induce complete remissions of relapsed leukemia in the absence of GVH disease [15]. Falkenburg and colleagues also showed that HLA class II up-regulation during viral infection can cause HLA DP-directed GVH disease after allogeneic donor CD4+ donor lymphocyte [16]. This finding is preluded many years earlier by the bone marrow transplantation pioneer Dick van Bekkum, who showed that inflammation accompanying graft versus host disease was suppressed in germfree animals [17]. The crucial importance of the gut microbiome in many immunological processes, varying from anti-influenza immunity to auto-immune disease susceptibility, has come to light in recent years, but was predicted by the Van Bekkum results. Recently Van Rood and colleagues have shown that re-exposure of cord blood to non-inherited maternal HLA antigens improves cord blood transplant outcome in hematological malignancies [18] and that maternal microchimerism in cord blood mediates a GVL effect in cord blood transplantation [19].

4. MHC expression and antigen processing by cancer cells

Traditionally cancer immunology in The Netherlands has appreciated the value of preclinical experimentation including scrutiny of basic immunological mechanism of importance for cancer immunology. In 1983 Peter Schrier, Rene Bernards and Kees Melief showed that adenovirus-induced tumors in mice could escape from T cell mediated immunity by downregulation of MHC class I expression on transformed cells [20,21]. This immunity escape mechanism was later shown in numerous human cancer studies. Ton Schumacher and Hidde Ploegh showed that MHC class I molecules on cancer cells with a TAP processing defect bind to peptides of a precisely defined length [22]. Later on Thorbald van Hall and Rienk Offringa showed that cancer cells with such a processing defect present a unique repertoire of TAP-independent CTL epitopes on both classical MHC class I molecules and non-classical Qa-1 class-I molecules [23,24]. Erik Reits and Jacques Neefjes discovered that the major substrates for TAP in vivo are derived from newly synthesized proteins [25]. Neefjes and colleagues, with the help of a genome-wide multidimensional RNAi screen, also revealed the existence of multiple pathways controlling MHC class II expression [26]. Another major finding of Neefjes and colleagues was that radiation therapy modulates the peptide repertoire in combination with enhancement of MHC class I expression, associated with successful induction of antitumor immune responses [27], an early study of major importance for the current interest in combinations of radiation therapy and immunotherapy in the clinic. In agreement with this, Toos Daemen and associates have demonstrated synergy between therapeutic vaccination and local low dose tumor irradiation [28].

5. Discovery of novel adhesion molecules and DC function

Yvette van Kooyk and Carl Figdor showed that T cell triggering through CD2 or CD3 regulates the activity of the important adhesion molecule LFA-1 [29] Theo Geijtenbeek, Yvette van Kooyk and Carl Figdor for the first time identified DC-SIGN, a dendritic cell (DC)-specific ICAM-3 receptor supporting primary immune responses [30,31]. Gosse Adema and colleagues identified a DC-derived C-C chemokine preferentially attracting naïve T cells and DC-SCRIPT, a novel DC-expressed member of the zinc finger family of transcriptional regulators [32,33]. Stefan Nierkens and Gosse Adema established that the immune adjuvant activity of CpG in cancer treatment is based on TLR9 function in plasmacytoid DC [34].

6. Discovery and function of the CD27 molecule on T cells

The CD27 TNF receptor family member CD27 was discovered by Rene van Lier in 1987 [35]. He an Jannie Borst have subsequently unraveled the function of CD27 in T and B cell biology, amongst others establishing that agonist antibody against

[1] Ph. Rümke and SP Israëls 2nd Eur. Congress on clinical oncology and cancer nursing, 1983.