Immunosurveillance and the importance of CD4 T-cells in cancer

The immune-oncology field has emerged based on a concept called cancer immunoediting which describes the dual role of the immune system, both providing protective immunity against malignancies but also shaping and even promoting tumour growth[1]. This whitepaper focuses on how the immune system causes successful tumour remission thereby emphasising on the crucial role of CD4 T-cells and the MHC class-II pathway.

IMMUNOSURVAILLANCE – an interplay of the innate and adaptive immune system

Immunosurveillance involves the processes by which immune cells scan the body for foreign pathogens, such as bacteria, viruses, but also cancer cells and eliminate them. Indeed, different immune cells are recruited upon cancer growth involving both innate immune cells (macrophages, NK-cells, and DCs) as well as adaptive immune cells (B-cells and T-cells)[2]. **Macrophages** are primarily phagocytes and are activated by cytokines produced by tumour cells or CD4+ TH1 cells to differentiate into tumouricidal M1-macrophages. On the other hand, **NK-cells** are designed to recognise cells that downregulate MHC-I expression to evade immune recognition such as cancer cells often exploit. Absence of MHC-I results in triggering the NK-cell and leads to lysis of the target cells via secretion of perforin and granzymes. In addition, both M1-macrophages and NK-cells produce pro-inflammatory mediators thereby inducing recruitment and activation of other immune cells such as dendritic cells (DCs).

Dendritic cells are the critical factor between the innate and the adaptive immune system as they are highly efficient in pathogen recognition (high expression of PRRs), uptake, processing, as well as antigen presentation and alongside in providing the necessary signals for optimal activation of lymphocytes. Upon recognition and uptake of tumour antigens, DCs maturate due to stimulation of the PRRs and process the antigen followed by presentation of the resulting oncopeptides on their cell surface via MHC-I or MHC-II[3,4]. The latter is necessary to activate the adaptive immune system. DCs can **provide the necessary three signals to activate T-lymphocytes**[5,6]. Indeed, CD4+ and CD8+ T-lymphocytes are primed upon recognition of MHC-oncopeptide complexes by their T-cell receptor and are alongside activated through cytokine secretion as well as by co-stimulation of their CD28 receptor by CD80 or CD86 present on the DC surface. This ultimately leads to clonal expansion of the T-lymphocytes. Depending on the cytokine profile different subsets are activated, i.e. CD4+ T-helper cells (TH1 or TFH), CD4+, and CD8+ T-effector cells as well as T-memory cells, all with their own task in building a strong anti-tumour response.

CD8+ T-effector cells or cytotoxic T-lymphocytes (CD8+ CTLs) **and CD4+ CTLs** are specialised in recognising MHC-oncopeptide complexes presented on tumour cells for which they are primed for by the DCs. This leads to the destruction of their target through apoptosis induction or lysis via secretion of cytotoxins. Whereas CD8+ effector cells recognise MHC-I-antigen complexes, the CD4+ T-cells focus on MHC-II-peptide complexes[7,8].

Next to T-effector cells, **T-memory cells** are also induced which are essential for prolonged protection against relapse and/or metastasis. On the other hand, CD4+ T-helper cells provide help to immune cells and aid the development of an all-embracing anti-tumour response. **CD4+ TH1 T-cells** facilitate CTL- as well as macrophage-mediated killing of tumour cells, induce immune cell recruitment, and provide help in CD8+ T-memory cell differentiation, expansion, and maintenance[9-11]. In addition, **follicular helper T-cells** (TFH) interact with B-cells and promote their differentiation into B-memory cells as well as plasma cells which in turn secrete antibodies (Ab) that can bind the oncopeptides presented on the tumour cell surface for which they are primed for. This binding evokes Ab-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) both leading to cancer cell lysis[9,12,13].

Altogether, it is clear that a wide network of different immune cells works together in order to achieve tumour eradication (see **Figure 1**). The overall result is tumour cell lysis or apoptosis which in turn evokes the release of endogenous danger signals (DAMPs), cytokines, and cancer antigens within the vicinity of the tumour. This enhances the immunogenicity of the tumour microenvironment as this leads to recruitment and activation of immune cells against other antigens which further fortifies and broadens the anti-tumour immune response[14-16].

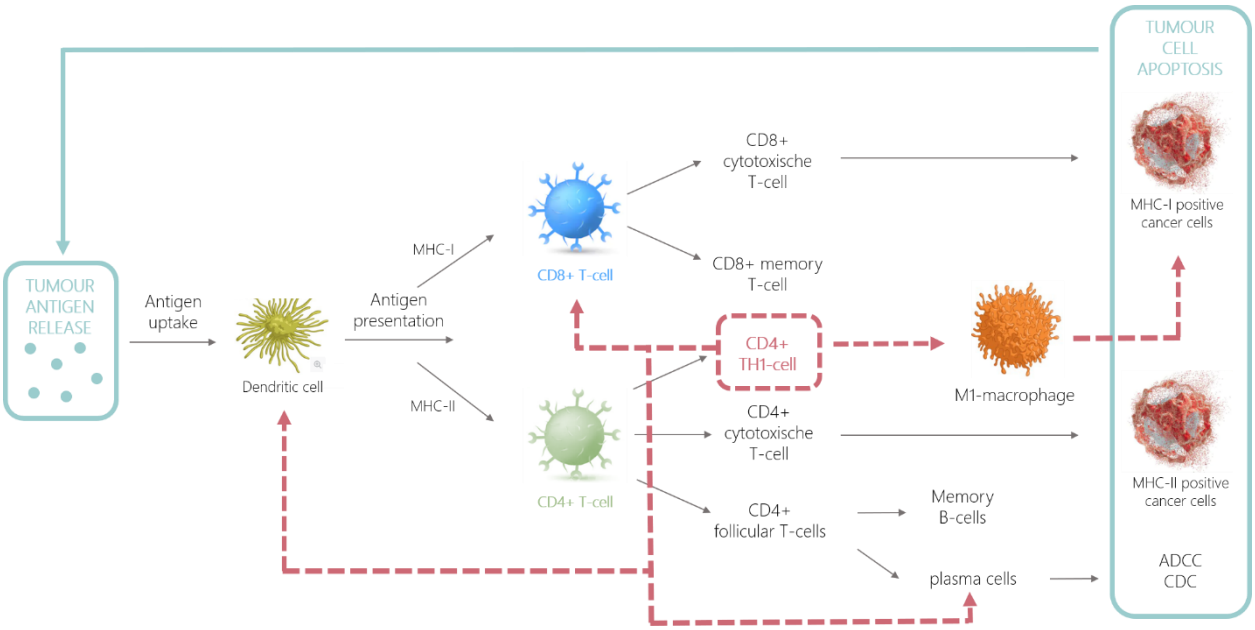

Figure 1. Overview of how tumour eradication is achieved by the immune system

THE IMPORTANCE OF CD4 T-CELLS

A distinction should be made in the different pathways that MHC-I versus MHC-II-bound oncopeptides evokes upon binding with T-cells. It was believed earlier that the MHC-I pathway was the main driver in anti-tumour immunity, however, it has been shown that the MHC-II pathway is of equal importance.

MHC-I-oncopeptide presentation by antigen-presenting cells (APCs) is necessary to activate CD8+ T-lymphocytes. Dendritic cells mainly drive the CD8+ T-cell activation as they are the most efficient APCs next to macrophages which also have antigen-presenting capabilities, however, to a lesser extent as their primary function is phagocytosis[16]. The **MHC-I pathway** is crucial as upon successful T-cell activation this **leads to proliferation into CD8+ CTLs** which are highly efficient in recognising and eradicating tumour cells that present these oncopeptides for which they are primed for via MHC-I on their cell surface[8]. The latter also explains why it was long believed that CD4+ T-cells cannot induce tumour cytolysis and the MHC-II pathway was thought to be not that important as the majority of the malignancies lack MHC-II expression[9].

Indeed, as CD4+ T-cells only recognise MHC-II-peptide complexes it was assumed that CD4+ T-lymphocytes do not have tumouricidal functionality. However, it has been shown that **CD4+ T-cells have both indirect and direct effector functions**. Indeed, CD4 T-cells can directly eradicate tumour cells provided that they are MHC-II-positive. In addition, it was shown that CD4+ T-cells can also indirectly be tumouricidal in cancers that lack MHC-II expression. This is possible due to the secretion of tumour antigens by cancer cells followed by processing and presentation of the oncopeptide onto MHC-II in antigen-presenting cells like DCs or macrophages in the tumour-draining lymph nodes[17]. Recognition of this MHC-II-peptide complex by CD4+ T-cells leads to activation and polarisation into CD4+ TH1 cells which can in turn indirectly induce cytolysis by stimulation of M1-macrophages and plasma cells which enhances their cytolytic function and their production of opsonising antibodies respectively[7, 18]. In addition, CD4 TH1 cells recruit innate immune cells as well as activate dendritic cells and license them into efficient induction of CD8 memory T-cells[19]. An overview of how

tumour eradication is achieved by the immune system highlighting the prominent role of CD4+ TH1 cells is illustrated in **Figure 1**.

Aside from these newly found direct and indirect effector functions of CD4+ T-cells, this subset has **also a broad spectrum of helper functions** that are already described above which are highly important to obtain a strong and long-lasting immune response. Without CD4+ TH1 cells, the efficacy and duration of the effector function of CD8+ CTLs would not be optimal due to the lack of TH1 cytokine stimulation[2, 10, 20] and no CD8+ T-memory cells would be formed as well[9-11]. In addition, TFH cells can activate a humoral response through interaction with B-cells. Following uptake, processing, and presentation onto MHC-II of tumour antigens on the B-cell surface, this complex is recognised by TFH cells stimulated by the same antigen. TFH cells offer additional stimulation of B-cells which induces in turn proliferation and differentiation into plasma cells and B-memory cells[9,12]. The combination of these functions clearly shows that the MHC-II pathway is of utmost importance in developing a strong immune response.

To conclude, both the innate and adaptive immune system work in close collaboration together and, in case of the adaptive immune response, both CD4+ and CD8+ T-cells are needed[21,22] to ultimately result in a broad and durable anti-tumour response. In the case of personalised cancer vaccination, this is very important to consider as targeting only CD8 oncopeptides could result in a suboptimal immune response that is not strong enough and does not evoke a long-lasting memory response.

About myNEO

myNEO (Ghent, Belgium) developed a platform enabling genomic-informed drug discovery in the key therapeutic areas of oncology and immunology. The data-driven ImmunoEngine identifies the most efficacious targets (epitopes) for each cancer patient, uniquely presented on the tumour cells and capable of redirecting a patient's immune system, leading to elimination of the cancer cells. The discovery platform enables targets to be identified even in hard-to-treat tumours with a cold/lowly mutated profile. Similarly, the company has applied its technology to identify immunogenic sequences in infectious diseases, capable of protecting populations with strong broad immune responses. myNEO is one of the companies that emerged from the Novalis biotech incubator fund at the end of 2018, founded by two leading entrepreneurs already known for several successes in the biotech industry: Wim Van Criekinge, professor of computational biology at Ghent University, and childhood friend Jan Van den Berghe.

Contact us

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