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Antigen-Presenting Cells: Potential of Proven und New Players in Immune Therapies

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The immune system is permanently confronted with mutated and self-, microbe-, and tumor-derived neoantigens – as well as other, "unknown" antigens – and has to differentiate between self or nonself. These antigenic molecules (protein or lipid based) must be phagocytosed, processed, and/or presented in the respective major histocompatibility complex (MHC) molecules on the cell surface in recognizable form to train immune cells such as effector T cells, leading to their specific activation. These "trainers" are so-called antigen-presenting cells (APCs), which can be divided into professional (e.g., dendritic cells [DCs], B cells, and macrophages) and nonprofessional APCs (e.g., fibroblasts and hepatocytes). While all nucleated human cells can present peptide fragments of endogenous proteins using the MHC class I pathway and display them on the surface to CD8+ cytotoxic T lymphocytes [1–3], only professional APCs such as DCs, macrophages, and B cells are characterized by the ability to present exogenous antigens using MHC class II molecules and present them on MHC class II molecules to CD4+ T-helper cells (T_H cells), along with the required costimulatory molecules, such as CD86 and CD83 molecules [2]. Therefore, the main difference between professional and nonprofessional APCs is the absence of MHC class II and costimulatory molecules on nonprofessional APCs. Recently, it was described that the three main granulocyte subsets (neutrophils, eosinophils, and basophils) also seem to be able to present exogenous antigens to naive T_H cells via MHC class II molecules, which has led to the suggestion that they should be referred to as APCs [4, 5].

Only professional APCs provide all three signals (antigen presentation via MHC molecules, expression of costimulatory molecules, and cytokine/chemokine secretion) needed to train and activate T cells to recognize, destroy, or tolerate cells that carry these antigens, and thereby to control viral infections or cancer cell growth [6, 7]. Macrophages and DCs internalize pathogens and cellular debris by phagocytosis, whereas B cells use the B-cell receptor for antigen uptake. Antigens are presented to T cells along with the required costimulatory molecules to get activated, get "licensed" to mediate their (helper or cytotoxic) function, and produce memory cells.

DCs are most effective at presenting tumor and viral antigens of intracellular origin because they have the ability to "cross-present" antigens [8]. A variety of DC subtypes in various organs with different phenotypical and functional characteristics mediating wound healing, proinflammation, or anti-infectious or antitumor attack were described, and they can be used for immune profiling to monitor the grade of activation or suppression of the immune system [9, 10]. Plasmacytoid or special tolerogenic DCs regulate responses of the innate and adaptive immune cells and contribute to avoiding autoimmune reactions [10–12].

DC-based treatments have been applied for almost three decades and so far have been tested most often in patients with malignant melanoma, prostate cancer, malignant glioma, or renal cell cancer [13, 14]. DCs were also applied in combination with cytokine-induced killer cells to treat gastrointestinal tumors, lung cancer, and breast

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cancer, as well as hematological malignancies [15]. Their clinical effectiveness was markedly increased after methods for generation, cultivation, and manipulation to exploit the immune-activating potential of DCs had been improved [14, 16]. The protocols were substantially improved with respect to optimization and standardization to increase cell yield, reduction of culture time, the differentiation process, and antigen loading. Recently, it was described that reprogramming of monocytes with lentiviral vectors expressing granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-α, interleukin (IL)-4, and antigens will lead to maturation of DCs and the induction of autocrine and paracrine immune effects against virus- or leukemia-associated antigens [17, 18].

A specialty of myeloid leukemic blasts is their capability to differentiate into "leukemia-derived DCs" [19–22]. Those DCs can either be generated ex vivo or used for adoptive transfer to patients with leukemia. Alternatively, blasts in the body can be converted into leukemia-derived DCs after treatment with approved drugs. This strategy is successful independent of patients' leukemic subtype, mutation, MHC expression, or transplantation status.

Macrophages, derived from the same progenitor cells as DCs, express MHC class II and costimulatory molecules after activation by IFN-γ. They also circulate in the blood and enter sites of infections or tissue damage and have been shown to be involved in cross-presentation of antigens [23]. Macrophages can be generated in vitro from monocytes or CD34 progenitor cells in the presence of cytokines such as M-CSF and GM-CSF, but a great heterogeneity in origin and tissue-specific functions was found, making the standardization of protocols more difficult. Protocols for generating APCs and macrophages as off-the-shelf products from induced pluripotent stem cells are under investigation, and they might open up a new field for generating and designing macrophages on a large scale to be used for clinical studies [24, 25].

To overcome limitations to the generation of conventional APCs – especially for cancer patients, where the functionality of both APCs and effector cells is impaired – alternative strategies are under investigation. Engineered MHC class I-deficient K562 cells or paramagnetic nanoparticle-based artificial (a) APCs were designed to optimize and control T-cell signals required for activation, expansion, and costimulation via human leukocyte antigen-restricted peptide complex and costimulatory signals [26, 27]. These tools make the generation of APCs cost-effective, highly reproducible, and scalable, and generated T-cell products will be capable of generating potent and durable responses in treated patients [28–30]. Interestingly, genetically modified K562-based aAPCs were recently used as an inexhaustible source for CD19-directed chimeric antigen receptor (CAR) T-cell expansion, thereby opening up new areas of APC application [31]. This approach was found to be less prone to variability in CAR T-cell expansion than a standard bead-based approach, and it resulted in CAR T cells with potent antitumor responses in preclinical models of acute lymphoblastic leukemia and B-cell lymphoma.

The knowledge of APCs' biology, their function and regulation, and their role in a pathological context (e.g., during the course of infection, allergy, autoimmunity, transplant rejection, or tumor immunological processes) is indispensable when utilizing APCs for clinical applications. In summary, highly professional APCs for cellular therapies can be generated or addressed by

- optimization of culture conditions for APCs and production under GMP (Good Manufacturing Practice) conditions [16, 22];
- generation of new, highly specialized APCs after loading with tumor antigens or generation of leukemia-derived APCs from myeloid blasts ex vivo [16];
- in vivo production of leukemia-derived DCs from blasts in the body [22];
- genetic engineering of precursors for APC generation [18, 25];
- usage of off-the-shelf APCs (DCs or macrophages) generated from induced pluripotent stem cells [25]; and
- establishment of aAPCs such as nanoparticles under highly reproducible conditions [30].

Our understanding of the mechanisms involved in antigen processing and presentation will be leading to effective and durable cellular and humoral immune responses and will contribute to the design of new vaccination strategies against microbial or tumor targets, to refinement of immune monitoring, to blockage of APC-mediated "overactivation" of the immune system, and to the development of attractive and useful accessories for improvement of new cell-based therapies.

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