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MGN1703, an immunomodulator and toll-like receptor 9 (TLR-9) agonist: From bench to bedside

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Abstract

The adaptive immune system has been the main focus of immunological strategies in oncology with only more recent approaches targeting innate immunity. Endosomal toll-like receptors (TLR-7, TLR-9) activate innate immune responses by signaling damage-associated molecular patterns (DAMP) from decaying tumor cells. This has led to the development of DNA-based TLR-9 agonists, which induce antitumor activity through innate and subsequent adaptive immune responses. Early clinical trials with CpG-ODN as TLR-9 agonists were associated with unfavorable tolerability and narrow clinical efficacy, leading to failure in pivotal trials. dSLIM®, the active ingredient of MGN1703, is a DNA-based, radically different molecular alternative to CpG-ODN, which results in genuine antitumor immunomodulation. Preclinical and

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clinical studies of MGN1703 have confirmed that this TLR-9 agonist has therapeutic potential in a variety of solid tumors, while long-term treatment with high doses was very well tolerated. A pivotal trial of first-line maintenance treatment with MGN1703 in patients with metastatic colorectal cancer is underway.

Keywords: Innate immune response; Toll-like receptor 9; dSLIM®; MGN1703; Anti-cancer immunomodulation; Colorectal cancer

1. Introduction

There is a growing recognition that the immune system plays a key role in the regulation of tumor growth and development. Components from both the innate and adaptive immune systems are involved and cell types such as natural killer cells (NK), natural killer T cells (NKT), dendritic cells (DC), macrophages, polymorphonuclear leukocytes, mast cells, myeloid-derived suppressor cells, T lymphocytes and B lymphocytes all have roles to play [1,2]. Some of these components inhibit the growth of cancer cells, resulting in their eventual death in a process known as immunosurveillance [3,4], however, others promote tumor development leading to a complicated balancing act between pro- and antitumor immunity (Table 1) [1,3].

This dual, and seemingly contradictory, functionality of the immune system was initially described by the immunoediting hypothesis, which included three phases: elimination, equilibrium and escape [5]. During the elimination phase, both an innate and adaptive immune response is triggered which may eliminate the tumor, whilst during the equilibrium phase, those cancer cells which were not eliminated persist in dynamic interaction with the immune system. Finally, the escape phase represents a period when tumor cells evade elimination by the immune system and the cancer progresses [5]. More recently the cancer stem cell, or the tumor initiating cell (TIC) hypothesis model has been described. Here, a small subfraction of TIC form a homogeneous stem cell-like population driving tumor maintenance and metastatic formation [6]. Evidence also suggests that TIC are not static, but can evolve and acquire additional genetic mutations and epigenetic modifications resulting in subclones, which consist of functionally different cells. Such functional diversity could also contribute to drug resistance, with chemotherapy leading to a selection of cells conferring survival advantages [6].

Table 1
Innate and adaptive immune cells involved in regulating tumor growth [1,3].

Stimulate cancer growth	Inhibit cancer growth
Innate immune cells	
Neutrophils	DC
Macrophage (M2)	Macrophage (M1)
Myeloid-derived suppressor cells	NK cells
Adaptive immune cells	
Th2 CD4+ T cell	Cytotoxic CD8+ T cell
CD4+ T regulatory cell	Th1 CD4+ T cell
	Th17 CD4+ T cell
Bridge both innate and adaptive systems	
NKT (type 2)	NKT (type 1)

DC, dendritic cell; NK, natural killer; NKT, NK T cells; Th, T-helper.

A number of immunologic approaches to treat cancer are based around activation of the endogenous adaptive immune response. One example is passive immunization, or adoptive cell therapy (ACT), which involves the transfusion of autologous or allogeneic T cells into a patient [7]. A variety of ACT methods are under investigation and the most developed of these is termed tumor-infiltrating lymphocyte (TIL) therapy [8]. Tumor-specific T cells are harvested from a biopsy specimen and cultured in vitro in the presence of interleukin (IL)-2 to promote growth. Following chemotherapy and/or radiotherapy to eradicate circulating lymphocytes, the patient receives a transfusion of the cultured T cells which can then induce a concerted antitumor response [7]. TIL therapy has shown promise in the treatment of metastatic melanoma [9]. Other methods of ACT are currently in development and clinical trials are ongoing in a wide range of cancers [10].

Active immunization through vaccination is another approach and encouraging results have been seen in prostate cancer with the vaccine sipuleucel-T. This immunotherapy product is prepared using a patient's own antigen presenting cells (APC), which are harvested and cultured ex vivo with a prostate antigen-containing fusion protein PA2024. T-cell immunity to the prostate antigen is induced via inclusion of granulocyte-macrophage colony-stimulating factor [11,12]. Two studies demonstrated that immunization with sipuleucel-T extended median overall survival (OS) in comparison to placebo [11,12], which led to Food and Drug Administration (FDA) approval of this cancer vaccine.

A third approach involves blocking regulatory checkpoints such as cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) or the programmed death-1 pathway and associated programmed death ligand 1 (PD-L1), which all limit the T-cell response and are therefore targets for cancer immunotherapy [13,14]. Fully human monoclonal antibodies directed against CTLA-4 have been developed, with the most widely studied being ipilimumab [15]. In patients with metastatic melanoma, this treatment has been reported to extend median OS [16], and ipilimumab has consequently been approved by the FDA for this indication. It is also being investigated in a variety of other cancers [15]. Development of a number of similar monoclonal antibodies is currently