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Review

Suppression of anti-cancer immunity by regulatory T cells: Back to the future

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Abstract

Suppressor/regulatory T cells were first shown to have an impact on cancer progression in experimental tumor models during the 1970s. However, the lack of specific markers hindered mechanistic investigations, and skepticism grew in the scientific community due to variability in cell populations and reported functions. The identification of regulatory $CD4^+CD25^+$ T cells has generated a great deal of renewed interest in cells that have immune regulatory properties. This article will provide a brief historical review of suppressor T cells and cancer, experimental and clinical evidence that $CD4^+CD25^+$ natural regulatory T cells play a role in cancer progression, and briefly discuss current strategies to inhibit these cells in an effort to enhance cancer immunotherapy.

Keywords: Suppressor T cell; Regulatory T cell; Cancer immunity

Contents

1. Introduction

Suppressor T cells, now almost exclusively referred to as regulatory T (T-reg) cells, were described more than three decades ago [1]. Reports directly implicating suppressor T cells in the progression of cancer were published as early as 1974 [2]. Identification of these cells in numerous experimental tumor models provided one explanation for why highly immunogenic tumors continued to grow in animals despite the generation of detectable anti-tumor immune responses. Reports in the 1980s continued to focus on identification and characterization of these cells in experimental tumor models. In parallel, it was recognized that cyclophosphamide treatment of patients could augment tumor immunity [3–5], apparently through the disruption of immune regulatory mechanisms including suppressor T cells. In 1986, Mukherji and colleagues identified immune suppressive T cells in lymph node (LN) tissue from a melanoma patient [6,7], which was the first report demonstrating the presence of suppressor T cells in human cancerous tissue. By 1990, interest in suppressor T cells had significantly waned due to the lack of suppressor T cell-specific markers and the confusing body of literature regarding their mechanisms of action, and scientists began to question their existence [8]. Due to the degree of skepticism that was generated during the 1980s, investigators today are hesitant to use the term “suppressor” T cells when referring to these cells, and the preferred terminology now is “regulatory” T cells.

Two experimental observations in the past 10 years have generated renewed interest in suppressor/T-reg cells. First, Sakaguchi and colleagues demonstrated that CD25, the alpha chain

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Table 1
Populations of suppressor/regulatory T cells

Designation	Phenotype/mechanism of suppression
Tr1	$CD4^+$; induced by culture with IL-10; suppress via IL-10 and TGF-β
Th2	$CD4^+$; regulatory functions involve the production of IL-4, IL-10, and IL-13
Th3/Tr3	$CD4^+$; secrete and suppress T cells via TGF-β
CD8	$CD8^+CD28^-$Foxp3+; generated after multiple rounds of stimulation in vitro, tolerize antigen-presenting cells $CD8^+\gamma\delta TCR^+$; appear to suppress immune reactivity via IL-10 and TGF-β
Veto Cells	$CD8^+$; suppress via Fas/FasL interactions
DN	$CD4^-CD8^-\alpha\beta TCR^+$; suppress via Fas/FasL interactions
NKT	$CD4^+$ or $CD4^-CD8^-$ cells expressing NK cell lineage markers, CD1d-restricted; immune regulatory functions may involve IL-4, IL-10, IL-13 and TGF-β as well as cell contact-dependent interactions
CD4	$CD4^+CD25^-Foxp3^+$; this population has been poorly characterized because of its low frequency $CD4^+CD25^+Foxp3^+$; "natural" T-reg cells, mechanism of action is unclear but it is cell contact-dependent

of the IL-2 receptor, was constitutively expressed on a subpopulation of murine $CD4^+$ T cells (∼5–10%) that exhibited potent immune suppressive activity both in vitro and in vivo [9]. Similar cells were subsequently identified in rats [10] and in human peripheral blood [11–15]. These $CD4^+CD25^+$ T cells were referred to as "natural" T-reg cells since they could be detected in freshly isolated lymphocyte preparations from normal animals or humans without any in vitro manipulations [16]. The second important observation was that the transcription factor Foxp3 plays a critical role in the development of $CD4^+CD25^+$ natural T-reg cells, and that the expression of Foxp3 is a highly specific marker for natural T-reg cells [17–19]. These two observations have convinced investigators that 'suppressor' T cells do exist, and there has been an explosion of literature focusing on the role of these cells in several settings including cancer immunity, autoimmunity, transplantation tolerance, allergic responses, and microbial immunity (reviewed in [16]). After much skepticism regarding the existence of suppressor T cells and their role in regulating immunity, investigators are now "back to the future" with renewed determination to find out whether these cells can be manipulated to influence various disease states in humans.

Several types of T cells have been shown to exhibit immune regulatory properties, including both naturally arising and induced populations of T cells (Table 1) (reviewed in [20,21]). This review will focus on $CD4^+CD25^+$ natural T-reg cells since they have been clearly implicated in suppression of immunity to cancer, they can be specifically identified in vivo, and because there is considerable optimism that functional inhibition of these cells will result in more effective anti-cancer immune therapies.

2. Suppressor/regulatory T cells and cancer: "the early years—pre 1995"

In 1974, Umiel and Trainin published data showing that thymocytes or splenic T cells taken from Lewis lung tumor (3LL)-bearing mice could enhance tumor growth in newly tumor injected syngeneic recipients [2]. Slower rates of tumor growth were observed in thymectomized recipients, providing further evidence that thymus-derived suppressor T cells played a role in tumor progression. Rotter and Trainin later showed that lethally irradiated mice given a syngeneic bone marrow transplant had an increased resistance to tumor challenge, and they proposed that the increased tumor resistance was due to a deficiency in suppressor T cells [22]; however, direct evidence for the presence of such cells was not provided.

In the 1980s, the majority of scientific papers implicating suppressor T cells in cancer came from North and colleagues [23–32]. In the early 1900s, it had been recognized that mice with progressively growing tumors could reject a second inoculation of the same tumor, a paradoxical phenomenon that was given the name 'concomitant tumor immunity' (reviewed in [33]). North and colleagues searched for evidence that suppressor T cells are involved in the progressive growth of immunogenic tumors, to help explain why tumor progression occurs in the face of concomitant immunity. Using a methylcholanthrene-induced fibrosarcoma, Meth A, they found that adoptive immunotherapy with tumor-sensitized T cells could induce regression of 6-day established tumors, but only if the tumor-bearing mice were T cell-deficient [32]. In further adoptive transfer experiments, it was found that Thy-1^+ suppressor T cells were responsible for the suppressive effect in immune competent tumor-bearing mice. These results were confirmed in the P815 mastocytoma tumor model, where it was also shown that the suppressive effect was tumor-specific [31]. Bear [34] went further to show that the suppressor T cells could suppress the generation of tumor-specific cytolytic T lymphocytes (CTLs) in vitro and that the suppressor T cells were radiation-sensitive.

To this point in time, the only marker that had been identified on tumor-induced suppressor T cells was Thy-1. In 1984, North and Bursuker, once again using the Meth A fibrosarcoma, showed that Ly-1^-2^+ ($CD8^+$) effector T cells responsible for mediating concomitant immunity were lost in tumor-bearing recipients after 9 days of tumor growth, and that this loss of effector cells was associated with the appearance of Ly-1^+2^- ($CD4^+$) suppressor T cells [30]. This was one of the first reports to implicate $CD4^+$ suppressor T cells in cancer progression. These results were confirmed in the P815 tumor model the following year [29]. Further evidence in support of $CD4^+$ suppressor T cells was provided through in vivo depletion experiments using CD4-specific monoclonal antibody (mAb) [25,27,35] and adoptive transfer experiments [24,35–37].

North [28] demonstrated the ability to eliminate suppressor T cells through administration of sublethal irradiation, confirming previous results reported by Hellstrom et al. [38]. Sublethal irradiation appeared to selectively eliminate cycling $CD4^+$ suppressor T cells while leaving $CD8^+$ anti-tumor effector cells intact, but timing of administration appeared to be critical, since irradiating tumor-bearing hosts too early also targeted developing anti-tumor effector T cells [26]. Of the five tumors examined, regression of 6-day established tumors was observed for three of the tumors (Meth A fibrosarcoma, SA-1 sarcoma, and L5178Y lymphoma) but not for the other two (P815 mastocytoma and