Promising γ-Chain Cytokines for Cancer Immunotherapy

Interleukins-7, -15, and -21 as Vaccine Adjuvants, Growth Factors, and Immunorestoratives

Terry J. Fry and Crystal L. Mackall

Summary

The molecular identification of a plethora of T-cell tumor antigens that can serve as targets for many human cancers, and the clinical development of techniques to administer tumor vaccines represent important advances toward the development of T-cell-specific immunotherapy for cancer. Despite this progress, current clinical results demonstrate that tumor vaccines, as single agents, are generally not potent enough to induce regression of existing tumors or long lasting enough to provide durable adjuvant benefit. Similarly, the full effectiveness of adoptive cellular therapies for cancer immunotherapy has not yet been realized because of difficulties in sustaining T-cells in vivo following adoptive transfer. Thus, the present challenge for the field of tumor immunology is to develop clinically applicable approaches for amplifying the T-cell-specific immunity induced by tumor vaccines and for augmenting survival of cells delivered in the context of adoptive therapies. The family of cytokines that signals through the common cytokine γ-chain (γc) demonstrates potent effects on T-cell development, expansion, and viability. Interleukin (IL)-2, a prototypic member of this family, has already demonstrated antitumor effects in some settings. However, recent studies have demonstrated that other members of the γc cytokine family possess characteristics that render them more favorable than IL-2 for amplifying T-cell-specific immunity toward tumors. IL-7, IL-15, and IL-21 have all shown promise in preclinical models of tumor immunotherapy. IL-7 is notable for its capacity to serve as an immunorestorative agent, as well as its ability to augment both CD4 and CD8 immune responses, with a particular capacity to amplify low-affinity, subdominant immune responses that are characteristically induced by tumor antigens. IL-15 provides potent survival and differentiation signals to both CD8 memory cells and natural-killer cells, features that are likely to be translatable in the context of both tumor vaccines and adoptive immunotherapy. IL-21 is less well studied than IL-7 or IL-15, but appears able to amplify responses to other cytokines, especially IL-15, thus further augmenting effector and memory cell expansion. Thus, a large amount of preclinical data suggest that integration of one or several new γc cytokines into immunotherapy regimens for cancer will play an important role in moving this field closer to clinical efficacy.

Key Words: IL-7; IL-15; IL-21; γc cytokines; T-cell homeostasis; adoptive immunotherapy; tumor vaccines; vaccine adjuvants.

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1. INTRODUCTION

Despite limited clinical success to date, there is continued optimism regarding the prospect of developing effective immunotherapy for cancer. This stems from advances at the basic science level, which have improved understanding of T-cell biology, and technological advances, which have provided new tools for clinical application. The insights into T-cell biology that pave the way for more effective cancer immunotherapy run the gamut from identification of a multitude of new tumor antigens to a better of understanding of T-cell co-stimulatory molecules and mechanisms of immune tolerance, to a more complete understanding of the factors that serve to maintain and/or disrupt T-cell homeostasis. The theoretical implications from all of this work continue to suggest that effective immunotherapy for cancer remains a realistic goal. However, despite the remarkable progress in bench research, major challenges remain in translating these tremendous insights to the clinic. New therapies must undergo stepwise preclinical development and iterative clinical testing to create regimens that can induce antitumor immunity that is potent and long lasting enough to clear established tumors and/or prevent tumor recurrence and specific enough to avoid autoimmunity.

Numerous clinical trials of tumor vaccines have demonstrated that measurable immune responses to a wide array of T-cell tumor antigens can be induced in most cancer patients, and that many different vaccine strategies, including genetic vectors, peptides, and dendritic cells (DCs), are effective at inducing measurable immune responses. Despite this progress, no tumor vaccine developed thus far has proved potent enough to reproducibly shrink established tumors and, whereas effectiveness in the adjuvant setting may ultimately be shown in some trials, it currently remains unproven. Thus, the consensus from these early trials is that tumor vaccines, as single agents, are unlikely to generate the robust immune responses required for immunotherapy of cancer (1). The next decade of work in tumor immunotherapy will seek to move beyond tumor antigen identification and testing of vaccines as single agents to the development of multimodality approaches that augment the strength and modulate the character of the immune responses induced by vaccination.

Cytokines are among the most promising agents available for potentiating weak immune responses induced by current tumor vaccines. As presented in Table 1, several cytokines are already approved for treatment in cancer patients, but most are aimed at improving supportive care and do not potentiate immunity per se. Interleukin (IL)-2 and interferon (IFN)-α2b are immunomodulatory cytokines with antitumor activity when used as single agents, but they are not active in the vast majority of cancer types, and the response rate to these agents remains low even in sensitive histologies. Further, whereas IL-2 can potentiate immune responses in some settings, a sizable body of evidence has demonstrated that, when compared with other cytokines in the same class, IL-2 is not especially well suited for enhancing T-cell immunity, because it predisposes to immune cell death and contributes to the induction of regulatory T-cells (2,3). Thus, the field of tumor immunology is awaiting anxiously the clinical availability of several new cytokines whose activity in preclinical models suggests that they will enhance immune responses toward tumor antigens. This chapter focuses on three cytokines currently under study that show promise for augmenting the effectiveness of T-cell and natural-killer (NK) cell-based immunotherapy for cancer: IL-7, IL-15, and IL-21. Like IL-2, signaling of each of these involves the common cytokine signaling γ-chain (γc) (Fig. 1), but as described in this chapter, each has unique properties that could be exploited in the context of cancer immunotherapy. We review basic biological properties of each agent and discuss the potential