SPRINGER REFERENCE

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Editor

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Encyclopedia of Cancer

2nd Edition

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one marrow examination or surgical excision or opsy of the suspected lesions

ment

ren with cancer are best cared for at a pediatric rehensive cancer care center that includes a team diatric oncologists, nurses, surgeons, radiation ogists, pathologists, and supportive care services e patients and their families. Treatment includes a ination of chemotherapeutic agents with or ut local radiation therapy and surgery. Chemo- y is usually given intravenously, intraspinally, nuscularly and by mouth. The specific agents nd on the disease being treated based upon 40 years nical trial experiences. Side effects include hema- ical toxicities (anemia, neutropenia and thrombo- enia), nausea and vomiting, alopecia, infections, ac, renal and liver toxicities depending on the otherapeutic agents used. Response to treatment is sed during therapy and treatment is adjusted based tumor response and patient side effects.

me and Late Effects

oved childhood cancer care including the develop- of combination of chemotherapeutic regimens, ortive care guidelines to minimize infection and ling resulted in a dramatic improvement in survival ure of most childhood cancers and a corresponding in the mortality rate (childhood cancer; Fig. 1). ever, physicians have become aware of late side ts to therapy that became apparent as early as s following completion of treatment up to several des later. Some of these side effects were related to cumulative dose of chemotherapy agents and ted in dose modification or replacement in newer nens to minimize immediate and late toxicity ut affecting efficacy. Similar modifications have made with radiation therapy by instituting niques to improve delivery of radiation to the r and minimizing damage to neighboring healthy es (involved field radiotherapy) as well as reducing otal dose of radiation delivered.

urrently, several pediatric oncology centers have lished clinics for childhood cancer survivors e they are followed for life. Patients are given ce about their risks of developing secondary ers, long term organ toxicities (cardiac, pulmonary,

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Chimeric

Definition

A mouse that carries a transgene in some tissues but not others; a mosaic animal.

►Mouse Models

Chimeric Antibodies

Definition

Hybrid immunoglobulins in which the original murine variable regions are preserved and the constant regions are switched for those of a human antibody to try to gain human effector functions. *Applications:* Antibody therapy when effector and other Fc-associated functions and properties are needed.

►Immunotherapy
►Diabody

Chimeric Antigen Receptor on T Cells

or more intracellular signaling endodomains, which can be genetically introduced into hematopoietic cells, such as T cells, to redirect specificity for a desired cell-surface antigen.

Characteristics

Background on Manipulating T-Cell Responses to Cancer

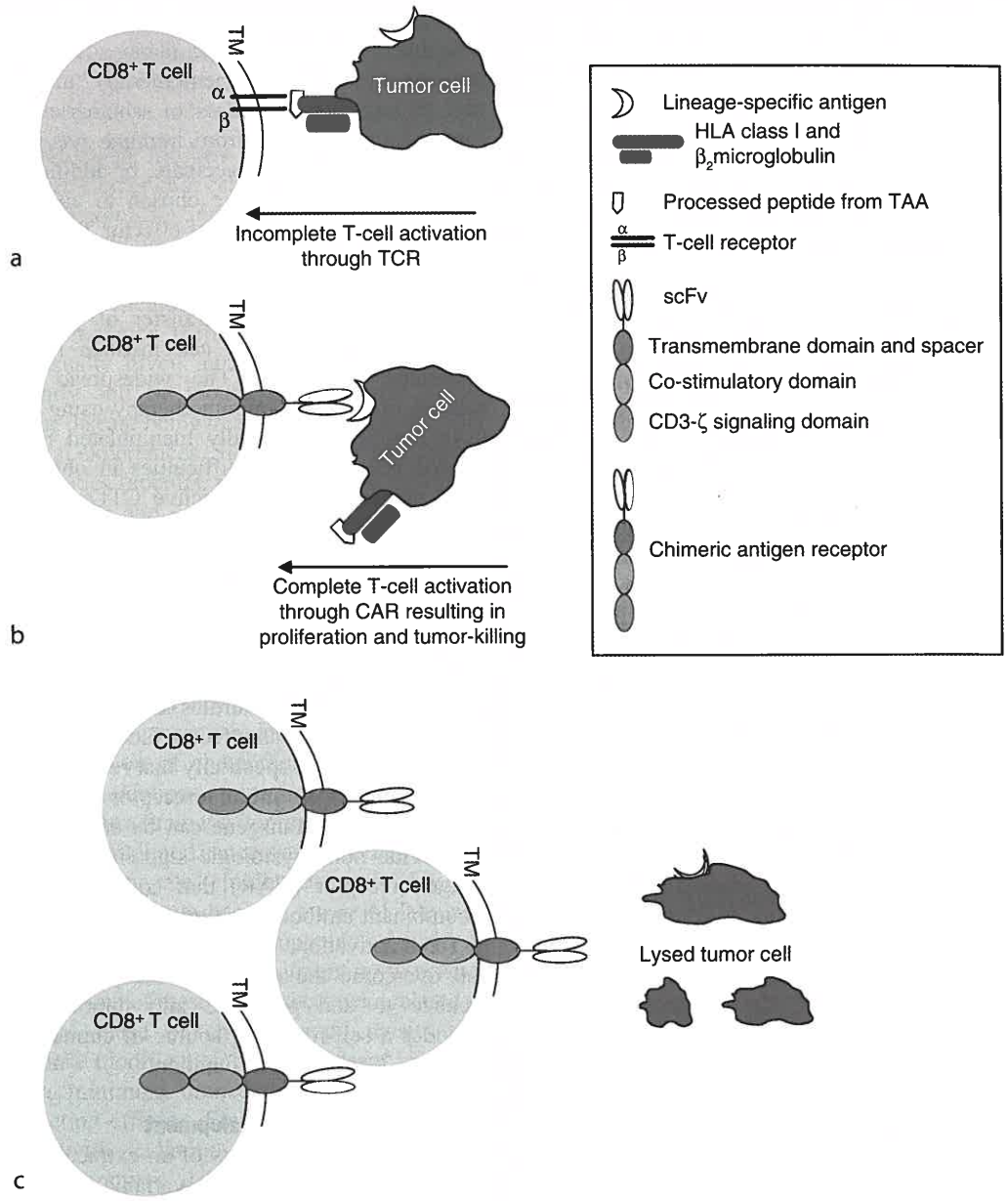
Adoptive transfer of tumor-specific T cells in mouse models can function as potent anti-cancer biological agents leading to elimination of established malignancies. Continued advances in tumor immunology support the premise and promise for ►adoptive immunotherapy as a treatment for human malignancies. Yet, infusion of tumor-specific T cells has only been partially successful in clinical oncology trials. Indeed, most of these trials demonstrate the safety and feasibility of infusing T cells, but with the exception of treating melanoma and chronic myelogenous leukemia (CML), only occasionally show a sustained anti-tumor effect. In contrast, infusing viral-specific T cells has successfully treated and protected patients from opportunistic diseases associated with adenovirus, CMV, and EBV. Why is it that augmenting an immune response against neoplasms by infusing tumor-specific T cells has proven more challenging than engendering an effective anti-viral response? The answer is partly due to the relative inability of T cells to recognize, via an endogenous T-cell receptor (TCR), poorly-immunogenic tumor-associated antigens (TAAs) compared with the highly-immunogenic/stimulatory viral antigens presented in the context of human leukocyte antigen (HLA). While TAAs generally have little or no expression in normal post-natal tissues outside of sanctuary sites, naturally-arising T cells are typically not reactive to tumors expressing a TAA due to immunologic tolerance. However, investigators have been able to manipulate T cells into recognizing TAA in the context of HLA molecules. This has been exploited by injection/infusion of (i) vaccines presenting TAA to overcome tolerance and stimulate T-cell immunity to tumors, (ii) tumor-specific T cells which have been culled from the patient and massively expanded in the laboratory, and (iii) T cells that have redirected specificity for tumor by genetically introducing pre-defined tumor-specific immunoreceptor genes. Clinical trials are currently evaluating all of three approaches.

While vaccines will likely have application for cancer prevention (►cancer vaccines), vaccination to eradicate nation, investigators have chosen to augment T-cell response through infusion of effector T cells (adoptive immunotherapy). Indeed, isolation, *ex vivo*-expansion of autologous tumor-infiltrating cytotoxic T-lymphocytes (CTLs), and subsequent transfer of these CTLs in lymphodepleted patients can mediate regression of metastatic melanoma. The widespread therapeutic success of adoptive immunotherapy using T cells that have not been genetically manipulated is, however, limited because of (i) difficulties in obtaining sufficient number of tumor-reactive CTLs from patients, (ii) TAAs are typically poor immunogens, (iii) existence of immune-regulatory mechanisms that prevent T-cell dependent reactivity against TAA (such emergence of tumor escape variants with loss of HLA), and (iv) the requirement that patients have pre-existing tumor-reactive cells that can be expanded *ex vivo*.

To overcome these hurdles investigators have combined the endogenous effector function of CTLs with re-directed antigen specificity that results from genetic introduction of an immunoreceptor. This introduced immunoreceptor transgene can be engineered *ex vivo* to provide non-physiologic signaling via a chimeric antigen receptor (CAR) that co-opts the ability of recombinant antibody to bind to tumor targets leading to T-cell activation. The development of CAR^+ T cells can overcome the relative inability of antibodies to localize to and penetrate into tumor masses and provides a self-renewing source of chimeric antibody linked to T-cell effector function.

Tumor-Specific CAR Development

Generally, a CAR consists of an extracellular domain composed of a single chain variable fragment (scFv) derived from a monoclonal antibody (mAb) against a cell-surface tumor-antigen which is typically a lineage specific molecule, such as CD19 on B cells. The scFv is typically suspended from the cell surface by a spacer (e.g. mAb Fc region) and uses a transmembrane (TM) region (e.g. from CD4 or CD28) to affix the scFv–Fc to the cell surface. This TM region is in turn fused in frame to one or more signaling modules that are normally present in an endogenous TCR signaling complex, such as the CD3-ζ chain (Fig. 1). The CAR can confer scFv-mediated antigen-recognition to T cells that is independent of HLA on tumor cells and endogenous TCR. T cells genetically modified to express a CAR can be propagated *in vitro* and demonstrated to exert robust CAR-dependent effector function. Upon antigen-mediated cross-linking of the CAR, the intracellular



Chimeric Antigen Receptor on T Cells. Figure 1 (a) Incomplete activation of T cells recognizing TAA through αβ TCR in context of HLA class I. (b) Fully-competent activation signal by T cells recognizing lineage-specific antigen (e.g. CD19) independent of HLA by introduced CAR. (c) Complete CAR-mediated activation results in T-cell proliferation and tumor lysis.

signaling domain or domains initiate cellular activation which can result in proliferation, cytokine secretion, activation upon antigen binding, manifesting appropriate T-cell effector mechanisms such as cytokine

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