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Receptor-targeted anticancer therapy

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Endoglin (ENG; CD105), an angiogenesis marker and ancillary TGF- β receptor

Introduction

ENG is a homodimeric cell membrane glycoprotein that was initially found on human leukemia cells and subsequently on endothelial cells [1, 2]. We possess five US and three foreign patents concerning ENG and related technologies. ENG is a proliferation-associated antigen of endothelial cells and expressed more abundantly on the vascular endothelium of tumor tissues than that of normal tissues. In addition, ENG is essential for angiogenesis and an ancillary transforming growth factor- β (TGF- β) receptor.

We have been studying ENG (a) as a target for therapy of cancer and other angiogenesis-associated diseases, (b) as a marker for diagnosis/prognosis of cancer, and (c) as an ancillary TGF- β receptor. A key tool in these studies is unique monoclonal antibodies (mAbs) that were generated and characterized in my laboratory. We generated 12 anti-ENG mAbs, termed SN6 series mAbs, and molecular locations of the epitopes defined by these mAbs were mapped. Antigen-binding avidity was determined for most of these mAbs. These mAbs reacted strongly with vascular endothelium of tumor tissues but less so with that of normal tissues. They did not react with tumor cells per se in the tissues [3, 4]. In addition, we found that soluble ENG is a useful marker for metastasis and tumor progression in breast, colorectal, and other cancer patients [5].

Suppression of angiogenesis, tumor growth, and metastasis, and mechanisms

The selected cross-reactive anti-ENG mAbs and their immunoconjugates suppressed angiogenesis in mice [3, 4]. They also suppressed growth of human tumors in severe combined immunodeficient (SCID) mice. In addition, they induced regression of preformed established tumors in SCID mice and strongly suppressed metastasis in tumor-bearing immunocompetent mice. In the immunocompetent mice, CD4⁺ and CD8⁺ T cells play pivotal roles in the anti-ENG mAb-mediated tumor suppression [6].

Mechanisms of the angiogenesis/tumor suppression by anti-ENG mAbs involve ADCC, direct suppression of proliferating endothelial cells, induction of apoptosis, cross-presentation, and modulation of signal transduction.

Clinical trials in cancer patients

A humanized (chimerized) anti-ENG mAb c-SN6j was generated in my laboratory. Pre-clinical pharmacokinetic and toxicology studies of c-SN6j were performed in non-human primates [7]. c-SN6j (also known as TRC105) was approved by FDA as an Investigational New Drug (IND) in a collaborative effort with a pharmaceutical company. In 2008, a multi-center phase I clinical trial was initiated in patients with advanced or metastatic solid cancer for whom curative therapy is unavailable. Although this clinical trial is still in progress, results of this trial are very promising.

Human B cell antigen receptor

Introduction

We previously discovered a novel heterodimeric cell membrane antigen that was strongly expressed on malignant B cells [8, 9]. This antigen was discovered by using three new mAbs termed SN8, SN8a, and SN8b that were generated in my laboratory. Amino acid sequence analysis revealed that this antigen is a human homolog of the $Ig\alpha/Ig\beta$ (mb-1/B29) component of the murine B cell antigen receptor complex [10]. At the 5th International Workshop and Conference on Human Leukocyte Differentiation Antigen (November, 1993), CD79a and CD79b were assigned to $Ig\alpha$ and $Ig\beta$, respectively. At this Workshop-Conference, SN8 was determined to be the only mAb that defines an extracellular epitope of CD79. We did not submit SN8a and SN8b to this Workshop-Conference. SN8 and SN8a react with CD79b while SN8b appears to react with CD79a. SN8 activates normal B cells but suppresses growth of malignant B cells. In addition, SN8 suppresses growth of B cell tumors in SCID mice. SN8 has been used for diagnosis of different B cell malignancies by many groups.

Therapeutic application of SN8

We are collaborating with a major pharmaceutical company to develop SN8 as a new therapeutic agent of patients with B cell malignancies. Researchers of the company generated several anti-CD79 mAbs, and they compared these mAbs with SN8 in several in vitro and in vivo (animal models) studies for potential therapeutic application. In each test, SN8 was superior to other mAbs [11]. Drug conjugates of SN8 were highly effective for eradicating B cell tumors in several animal models. We possess one US patent that is directly relevant to this clinical application.

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