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(54) **CHIMERIC RECEPTORS WITH 4-1BB STIMULATORY SIGNALING DOMAIN**

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(57) **ABSTRACT**

The present invention relates to a chimeric receptor capable of signaling both a primary and a co-stimulatory pathway, thus allowing activation of the co-stimulatory pathway without binding to the natural ligand. The cytoplasmic domain of the receptor contains a portion of the 4-1BB signaling domain. Embodiments of the invention relate to polynucleotides that encode the receptor, vectors and host cells encoding a chimeric receptor, particularly including T cells and natural killer (NK) cells and methods of use. Also included is a method for obtaining an enriched population of NK cells from a mixed population of NK cells and T cells.

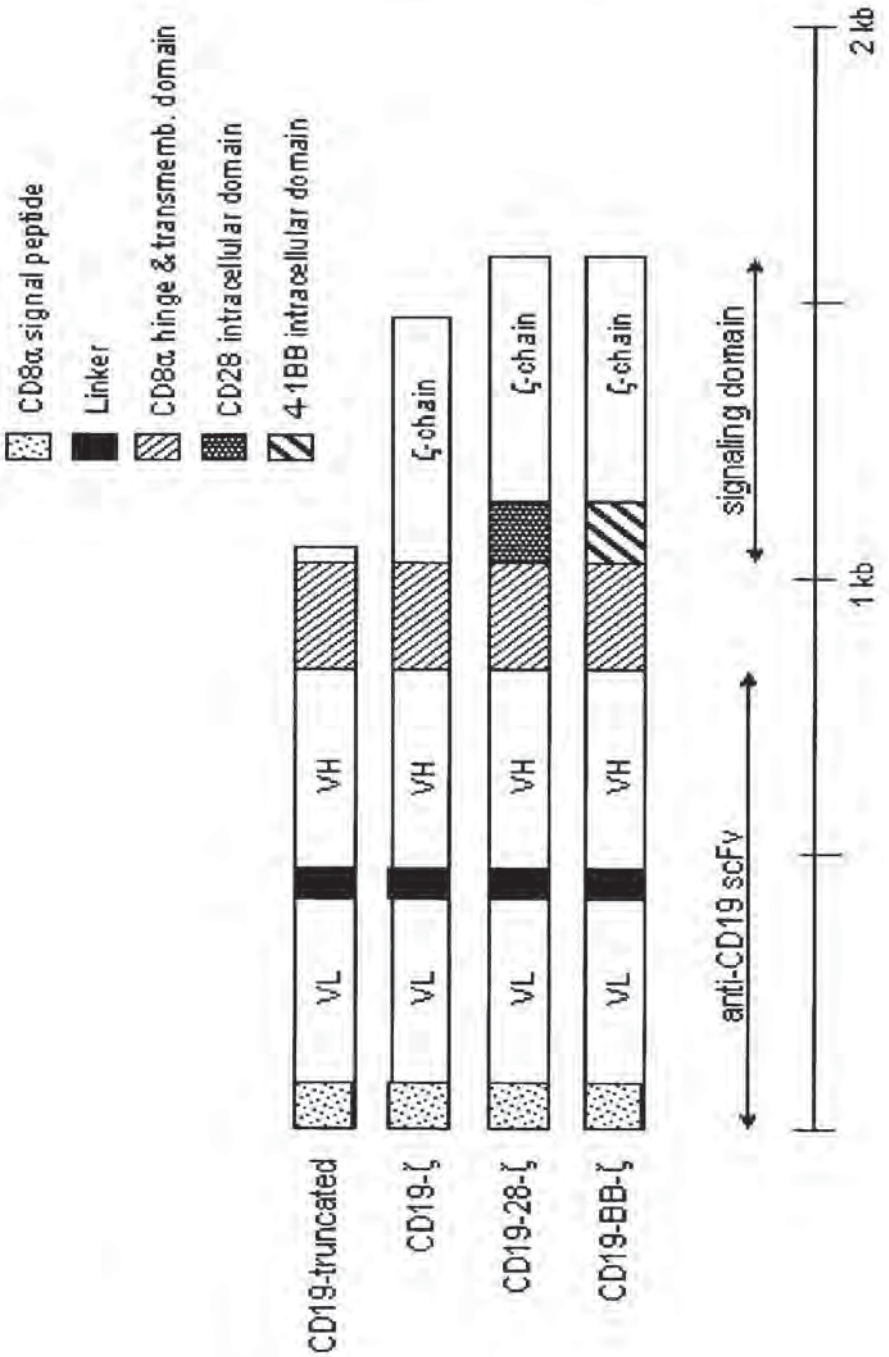

Figure 1

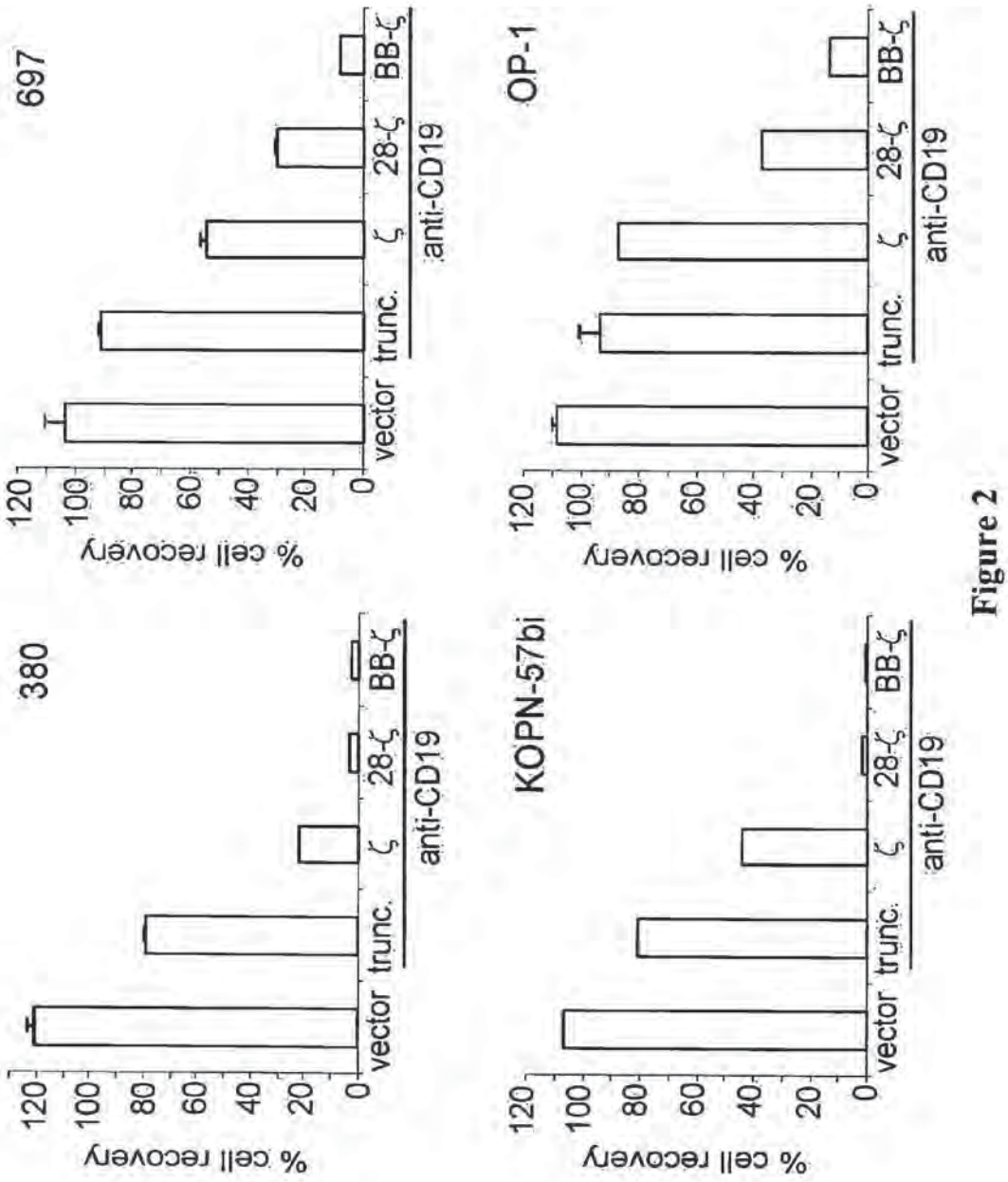

Figure 2

CHIMERIC RECEPTORS WITH 4-1BB STIMULATORY SIGNALING DOMAIN

GOVERNMENT INTEREST

[0001] This invention was made in part with U.S. Government support under National Institutes of Health grant no. CA 58297. The U.S. Government may have certain rights in this invention.

FIELD OF THE INVENTION

[0002] This invention relates to chimeric cell membrane receptors, particularly chimeric T-cell receptors.

BACKGROUND

[0003] Regulation of cell activities is frequently achieved by the binding of a ligand to a surface membrane receptor comprising an extracellular and a cytoplasmic domain. The formation of the complex between the ligand and the extracellular portion of the receptor results in a conformational change in the cytoplasmic portion of the receptor which results in a signal transduced within the cell. In some instances, the change in the cytoplasmic portion results in binding to other proteins, where other proteins are activated and may carry out various functions. In some situations, the cytoplasmic portion is autophosphorylated or phosphorylated, resulting in a change in its activity. These events are frequently coupled with secondary messengers, such as calcium, cyclic adenosine monophosphate, inositol phosphate, diacylglycerol, and the like. The binding of the ligand to the surface membrane receptor results in a particular signal being transduced.

[0004] For T-cells, engagement of the T-cell receptor (TCR) alone is not sufficient to induce persistent activation of resting naive or memory T cells. Full, productive T cell activation requires a second co-stimulatory signal from a competent antigen-presenting cell (APC). Co-stimulation is achieved naturally by the interaction of the co-stimulatory cell surface receptor on the T cell with the appropriate counter-receptor on the surface of the APC. An APC is normally a cell of host origin which displays a moiety which will cause the stimulation of an immune response. APCs include monocyte/macrophages, dendritic cells, B cells, and any number of virally-infected or tumor cells which express a protein on their surface recognized by T cells. To be immunogenic APCs must also express on their surface a co-stimulatory molecule. Such APCs are capable of stimulating T cell proliferation, inducing cytokine production, and acting as targets for cytolytic T cells upon direct interaction with the T cell. See Linsley and Ledbetter, Ann. Rev. Immunol. 4:191-212 (1993); Johnson and Jenkins, Life Sciences 55:1767-1780 (1994); June et al., Immunol. Today 15:321-331 (1994); and Mondino and Jenkins, J. Leuk. Biol. 55:805-815 (1994).

[0005] Engagement of the co-stimulatory molecule together with the TCR is necessary for optimal levels of IL-2 production, proliferation and clonal expansion, and generation of effector functions such as the production of immunoregulatory cytokines, induction of antibody responses from B cells, and induction of cytolytic activity. More importantly, engagement of the TCR in the absence of the co-stimulatory signal results in a state of non-responsiveness, called anergy. Anergic cells fail to become activated upon subsequent stimulation through the TCR, even in the presence of co-stimulation, and in some cases may be induced to die by a programmed self-destruct mechanism.

[0006] In certain situations, for example where APCs lack the counter-receptor molecules necessary for co-stimulation, it would be beneficial to have the co-stimulatory signal induced by virtue of employing a ligand other than the natural ligand for the co-stimulatory receptor. This might be, for example, the same ligand as that recognized by the TCR (i.e., the same moiety, such that if one signal is received, both signals will be received), or another cell surface molecule known to be present on the target cells (APCs).

[0007] Several receptors that have been reported to provide co-stimulation for T-cell activation, including CD28, OX40, CD27, CD2, CD5, ICAM-1, LFA-1 (CD11a/CD18), and 4-1BB. The signaling pathways utilized by these co-stimulatory molecules share the common property of acting in synergy with the primary T cell receptor activation signal.

[0008] Previously the signaling domain of CD28 has been combined with the T-cell receptor to form a co-stimulatory chimeric receptor. See U.S. Pat. No. 5,686,281; Geiger, T. L. et al., Blood 98: 2364-2371 (2001); Hombach, A. et al., *J Immunol* 167: 6123-6131 (2001); Maher, J. et al. *Nat Biotechnol* 20: 70-75 (2002); Haynes, N. M. et al., *J Immunol* 169: 5780-5786 (2002); Haynes, N. M. et al., *Blood* 100: 3155-3163 (2002). These co-stimulatory receptors provide a signal that is synergistic with the primary effector activation signal, i.e. the TCR signal or the chimeric effector function receptor signal, and can complete the requirements for activation under conditions where stimulation of the TCR or chimeric effector function receptor is suboptimal and might otherwise be detrimental to the function of the cell. These receptors can support immune responses, particularly of T cells, by permitting the use of ligands other than the natural ligand to provide the required co-stimulatory signal.

[0009] Chimeric receptors that contain a CD19 specific single chain immunoglobulin extracellular domain have been shown to lyse CD19+ target cells and eradicate CD19+ B cell lymphomas engrafted in mice [Cooper L J, et al., Blood 101:1637-1644 (2003) and Brentjens R J, et al., Nature Medicine 9:279-286 (2003)]. Cooper et al. reported that T-cell clones transduced with chimeric receptors comprising anti-CD19 scFv and CD3ζ produced approximately 80% specific lysis of B-cell leukemia and lymphoma cell lines at a 1:1 effector to target ratio in a 4-hour Cr release assay; at this ratio, percent specific lysis of one primary B-lineage ALL sample tested was approximately 30%. Brentjens et al. reported that T-cells bearing anti-CD19 scFv and CD3ζ chimeric receptors could be greatly expanded in the presence of exogenous IL-15 and artificial antigen-presenting cells transduced with CD19 and CD80. The authors showed that these T cells significantly improved the survival of immunodeficient mice engrafted with the Raji B-cell lymphoma cell line. Their results also confirmed the importance of co-stimulation in maximizing T-cell-mediated anti-leukemic activity. Only cells expressing the B7 ligands of CD28 elicited effective T-cell responses. This could be a major obstacle in the case of B-lineage ALL because leukemic lymphoblasts typically do not express B7 molecules.

[0010] In addition to T cell immune responses, natural killer (NK) cell responses appear to be clinically relevant. While T cells recognize tumor associated peptide antigen

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