CCR6

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SUMMARY

CCR6 is a seven transmembrane domain G protei2 n-coupled receptor for MIP-3α, a CC chemokine expressed by a variety of cell types, including epithelial cells, in response to inflammatory stimuli. CCR6 is expressed on memory T cells, B cells, and CD34+ bone marrow progenitor-derived dendritic cells. CCR6 is active on resting memory cells and can mediate both chemotaxis and adhesion of these cells to ICAM-1. It is presumed that CCR6 is involved in the recruitment of memory T cells at the initiation of a response at inflammatory sites and/or in reactive lymphoid tissue. Data also suggest that CCR6 on immature dendritic cells may be important for the recruitment of these cells to inflammatory sites. Since the MIP-3α gene is also expressed in dendritic cells, CCR6 may mediate aggregation of dendritic cells, memory T cells, and B cells.

BACKGROUND

Discovery

CCR6 was discovered by several groups as an orphan receptor as part of screening for new G protein-coupled receptors or specifically for new chemokine receptors. The first sequence entered in the database was a genomic sequence, GPR-CY4, and the first published sequences were a genomic sequence designated CKR-L3 (Zaballos *et al*., 1996) and cDNA and genomic sequences for a gene designated *STRL22* (Liao *et al*., 1997c). The protein encoded by this gene was described as a receptor for the chemokine LARC/MIP-3α/Exodus/CK-β4 by several groups (Baba *et al*., 1997; Liao *et al*., 1997a; Power *et al*., 1997; Greaves *et al*., 1997) and was thereby named CCR6.

Alternative names

None currently in use. Old names include GPR-CY4, CKR-L3, STRL22, DCCR2, BN-1, and DRY6.

Structure

Like other chemokine receptors, CCR6 is a seven transmembrane domain G protein-coupled receptor. CCR6 is predicted to be 374 amino acids in length.

Main activities and pathophysiological roles

CCR6 is a receptor for the chemokine LARC/MIP-3α/Exodus/CK-β4 (Baba *et al*., 1997; Greaves *et al*., 1997; Liao *et al*., 1997a; Power *et al*., 1997), a chemokine that, based on the expression of mRNA, is produced by activated macrophages, endothelial cells, and dendritic cells, and at some mucosal sites. CCR6 is expressed and functional on CD34+ bone marrow progenitor cell-derived dendritic cells (Greaves *et al*., 1997; Power *et al*., 1997; Liao *et al*., 1999), particularly on 'immature' dendritic cells early in their differentiation *in vitro* (Dieu *et al*., 1998), as well as on CD4+ and CD8+ T cells (Baba *et al*., 1997; Greaves *et al*., 1997; Power *et al*., 1997; Liao *et al*., 1999). In the case of T cells, CCR6 is expressed exclusively on those of the memory phenotype (Liao *et al*., 1999). CCR6 is also expressed on B cells (Zaballos *et al*., 1996; Baba *et al*., 1997; Liao *et al*., 1997b, 1999; Varona *et al*., 1998), and MIP-3α has been reported to be active on B cells from Peyer's patches (Tanaka *et al*., 1999). It is presumed that CCR6 is involved in the trafficking of dendritic cells and T cells, and perhaps B cells, particularly at mucosal sites.

GENE

Accession numbers

Human gene: U45985, Z79784, U68031
Human cDNAs: U68030, U68032
Mouse gene: AJ222714
Mouse cDNA (KY411): AB009369

The human CCR6 gene is on chromosome 6q27, a site without other known chemokine receptors (Liao *et al*., 1997c).

Sequence

See **Figure 1**.

PROTEIN

Accession numbers

Human: AAC51124
Mouse: BAA23776

Sequence

See **Figure 2**.

Description of protein

No information is available other than what can be predicted from the primary structure. CCR6 is

Figure 1 Nucleotide sequences for human and mouse CCR4.

Human gene:

AACTGTAGTGCATTTTGCCTTCTTTCCTTCTTAGAGTCACCTCTACTTTCCTGCTACCGCTGCCTGTGAGCTGAAGGGGCTGAACCATACACTCCTT
TTTCTACAACCAGCTTGCATTTTTTCTGCCCACAATGAGCGGGGTAAGATTTTTATTTTTGGCAAGGGGTATAATTTGGGTTCACTGTGGCTACTTG
AACACTACACTGCAGCTAACTCTATCTTTGTTTCCTTTCCAGGAATCAATGAATTTCAGCGATGTTTTCGACTCCAGTGAAGATTATTTTGTGTCAG
TCAATACTTCATATTACTCAGTTGATTCTGAGATGTTACTGTGCTCCTTGCAGGAGGTCAGGCAGTTCTCCAGGCTATTTGTACCGATTGCCTACTC
CTTGATCTGTGTCTTTGGCCTCCTGGGGAATATTCTGGTGGTGATCACCTTTGCTTTTTATAAGAAGGCCAGGTCTATGACAGACGTCTATCTCTTG
AACATGGCCATTGCAGACATCCTCTTTGTTCTTACTCTCCCATTCTGGGCAGTGAGTCATGCCACTGGTGCGTGGGTTTTCAGCAATGCCACGTGCA
AGTTGCTAAAAGGCATCTATGCCATCAACTTTAACTGCGGGATGCTGCTCCTGACTTGCATTAGCATGGACCGGTACATCGCCATTGTACAGGCGAC
TAAGTCATTCCGGCTCCGATCCAGAACACTACCGCGCAGCAAAATCATCTGCCTTGTTGTGTGGGGGCTGTCAGTCATCATCTCCAGCTCAACTTTT
GTCTTCAACCAAAAATACAACACCCAAGGCAGCGATGTCTGTGAACCCAAGTACCAGACTGTCTCGGAGCCCATCAGGTGGAAGCTGCTGATGTTGG
GGCTTGAGCTACTCTTTGGTTTCTTTATCCCTTTGATGTTCATGATATTTTGTTACACGTTCATTGTCAAAACCTTGGTGCAAGCTCAGAATTCTAA
AAGGCACAAAGCCATCCGTGTAATCATAGCTGTGGTGCTTGTGTTTCTGGCTTGTCAGATTCCTCATAACATGGTCCTGCTTGTGACGGCTGCAAAT
TTGGGTAAAATGAACCGATCCTGCCAGAGCGAAAAGCTAATTGGCTATACGAAAACTGTCACAGAAGTCCTGGCTTTCCTGCACTGCTGCCTGAACC
CTGTGCTCTACGCTTTTATTGGGCAGAAGTTCAGAAACTACTTTCTGAAGATCTTGAAGGACCTGTGGTGTGTGAGAAGGAAGTACAAGTCCTCAGG
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GCTGAGTCTCCCTAAGGCATGTGTGAAACATACTCATAGATGTTATGCAAAAAAAAGTCTATGGCCAGGTATGCATGGAAAATGTGGGAATTAAGCA
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ACAGAAAAAAAAAATGGAAGCCAACACATCACTCATTTTAGGCAAATGTTTAAACATTTTTATCTATCAGAATGTTTATTGTTGCTGGTTATAAGCAG
CAGGATTGGCCGGCTAGTGTTTCCTCTCATTTCCCTTTGATACAGTCAACAAGCCTGACCCTGTAAAATGGAGGTGGAAAGACAAGCTCAAGTGTTC
ACAACCTGGAAGTGCTTCGGAAAGAAGGGGACAATGGCAGAACAGGTGTTGGTGACAATTGTCACCAATTGGATAAAGCAGCTCAGGTTGTAGTGGG
CCATTAGGAAACTGTCGGTTTGCTTTGATTTCCCTGGGAGCTGTTCTCTGTCGTGAGTGTCTCTTGTCTAAACGTCCATTAAGCTGAGAGTGCTATG
AAGACAGGATCTAGAATAATCTTGCTCACAGCTGTGCTCTGAGTGCCTAGCGGAGTTCCAGCAAACAAAATGGACTCAAGAGAGATTTGATTAATGA
ATCGTAATGAAGTTGGGGTTTATTGTACAGTTTAAAATGTTAGATGTTTTTAATTTTTTAAATAAATGGAATACTTTTTTTTTTTTTTAAAGAAAGC
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AGATTAGCTAGGGGACAGCTGGAATTATGCTGGCTTCTGATAATTATTTTAAAGGGGTCTGAAATTTGTGATGGAATCAGATTTTAACAGCTCTCTT
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GGAGTTTGAGACCAGCCTGGCCAACATGGCGAAACCCCTCTCTACTAAAAATACAAAAATTTGCCAGGCGTGGTGGCGGGTGCCTGTAATCCCAGCT
ACTTGGGAGGCTGAGGCAAGAGAATCGCTTGAACCCAGGAGGCAGAGGTTGCAGTGAGCCGAGATCGTGCCATTGCACTCCAGCCTGGGTGACAAAG
CGAGACTCCATCTCAAAAAAAAAAAAAAAAAAAAAAAGGAAAGAACTGTCATGTAAACATACCGACATGTTTAAACCTGACAATGGTGTTATTTGAAA
CTTTATATTGTTCTTGTAAGCTTTAACTATATCTCTCTTTAAAATGCAAAATAATGTCTTAAGATTCAAAGTCTGTATTTTTAAAGCATGGCTTTGG
CTTTGCAAAATAAAAAATGTGTTTTGTACATGAAGTAGGAATCGTATTTCAGCTTCAAGGTTCAGATTGAGGGGCCCACTGTTTGGAGAGGATGGTA
TTCAGGCTTTCTCATGTCCTTCAAATCTGTTAGCGTTTGACTCTAGAAATCAAAGCAAAGGAGTGGTTACCCAGACACTTCTTTTGGTGTGATCAAT
GCGCTGATGTGATCTATGAAGATGATTCATGCTTGAAAACTAGCACAGAAACATCTTGCTTATTTGCCAAAGCTGGGAGATGAGCTTCTCTGCATAA
TTTAAATGTTCAGATAAATGAAGCTGACTTATTTAAGCAATAACCTTTTAAACATTTTAGCTAAGATGTATAAAAATGTTTCCAAAATATACCACAT
ACTTTATTTCTTCTTAAATGTAGTACATTAGGTTACATCATTTTTCTTGCTGTCTTGGGCATCAAAACAGGTGCCATGGTAACCTGACACTCTCAGG
AGACATTAAGATAGAAGGGGCTGTTCTTCAGTGGTTCCCATTGATTCTCCCCATATCTTTTTGCTCTCAGGCTCTGGCCGTCTCTTCCTGAGCCTTA
ACTGTGT

Figure 1 (*Continued*)

Human cDNA:

CAAACGTTCCCAAATCTTCCCAGTCGGCTTGCAGAGACTCCTTGCTCCCAGGAGATAACCAGAAGCTGCATCTTATTGACAGATGGTCATCACATTG
GTGAGCTGGAGTCATCAGATTGTGGGGCCCGGAGTGAGGCTGAAGGGAGTGGATCAGAGCACTGCCTGAGAGTCACCTCTACTTTCCTGCTACCGCT
GCCTGTGAGCTGAAGGGGCTGAACCATACACTCCTTTTTCTACAACCAGCTTGCATTTTTTCTGCCCACAATGAGCGGGGAATCAATGAATTTCAGC
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GGCAGTTCTCCAGGCTATTTGTACCGATTGCCTACTCCTTGATCTGTGTCTTTGGCCTCCTGGGGAATATTCTGGTGGTGATCACCTTTGCTTTTTA
TAAGAAGGCCAGGTCTATGACAGACGTCTATCTCTTGAACATGGCCATTGCAGACATCCTCTTTGTTCTTACTCTCCCATTCTGGGCAGTGAGTCAT
GCCACTGGTGCGTGGGTTTTCAGCAATGCCACGTGCAAGTTGCTAAAAGGCATCTATGCCATCAACTTTAACTGCGGGATGCTGCTCCTGACTTGCA
TTAGCATGGACCGGTACATCGCCATTGTACAGGCGACTAAGTCATTCCGGCTCCGATCCAGAACACTACCGCGCACGAAAATCATCTGCCTTGTTGT
GTGGGGGCTGTCAGTCATCATCTCCAGCTCAACTTTTGTCTTCAACCAAAAATACAACACCCAAGGCAGCGATGTCTGTGAACCCAAGTACCAGACT
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ATCTATCAGAATGTTTATTGTTGCTGGTTATAAGCAGCAGGATTGGCCGGCTAGTGTTTCCTCTCATTTCCCTTTGATACAGTCAACAAGCCTGACC
CTGTAAAATGGAGGTGGAAAGACAAGCTCAAGTGTTCACAACCTGGAAGTGCTTCGGGAAGAAGGGGACAATGGCAGAACAGGTGTTGGTGACAATT
GTCACCAATTGGATAAAGCAGCTCAGGTTGTAGTGGGCCATTAGGAAACTGTCGGTTTGCTTTGATTTCCCTGGGAGCTGTTCTCTGTCGTGAGTGT
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GCAAACAAAATGGACTCAAGAGAGATTTGATTAATGAATCGTAATGAAGTTGGGGTTTATTGTACAGTTTAAAATGTTAGATGTTTTTAATTTTTTA
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TTTGGGAAGCTAAGATGGGTGGATCACTTGAGGTCAGGAGTTTGAGACCAGCCTGGCCAACATGGCGAAACCCCTCTCTACTAAAAATACAAAAATT
TGCCAGGCGTGGTGGCGGGTGCCTGTAATCCCAGCTACTTGGGAGGCTGAGGCAAGAGAATCGCTTGAACCCAGGAGGCAGAGGTTGCAGTGAGCCG
AGATCGTGCCATTGCACTCCAGCCTGGGTGACAGAGCGAGACTCCATCTCAAAAAAAAAAAAAAAAAA

Mouse gene:

TCTGCTCTCCCAACATCTGCACTAGTGAGAGTGTGGTTGAACTGCCCACTTCCCTTTCTACACCAGATCTGGCTCTCCCATCCACATAGAGAACCAC
GCCTGCCTGGGGTGAGAATCTACTTTATCTTGGCAGGGACTCTGGCATGGCTAGGTGTGGTTGCTTGAAATCACACTGTCACGATTTCTATTTTCAT
TATCATTCAGGAATGAATTCCACAGAGTCCTACTTTGGAACGGATGATTATGACAACACAGAGTATTATTCTATTCCTCCAGACCATGGGCCATGCT
CCCTAGAAGAGGTCAGAAACTTCACCAAGGTATTTGTGCCAATTGCCTACTCCTTAATATGTGTCTTTGGCCTCCTGGGCAACATTATGGTGGTGAT
GACCTTTGCCTTCTACAAGAAAGCCAGATCCATGACTGACGTCTACCTGTTGAACATGGCCATCACAGACATACTCTTTGTCCTCACCCTACCGTTC
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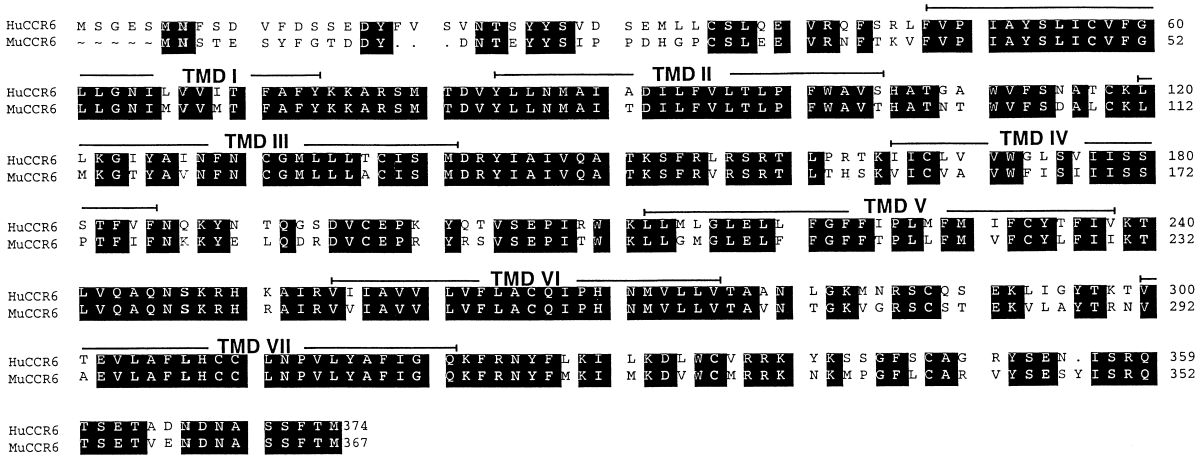
TGTTCTGCTATCTGTTCATTATCAAGACCTTGGTGCAGGCCCAGAACTCCAAGAGGCACAGAGCCATCCGAGTCGTGATCGCTGTGGTTCTCGTGTT
CCTGGCTTGTCAGATCCCTCACAACATGGTCCTCCTCGTGACTGCGGTCAACACGGGCAAAGTGGGCCGGAGCTGCAGCACCGAGAAAGTCCTCGCC
TACACCAGGAACGTGGCCGAGGTCCTGGCTTTCCTGCATTGCTGCCTCAACCCCGTGTTGTATGCGTTTATTGGACAGAAATTCAGAAACTACTTCA
TGAAGATCATGAAGGATGTGTGGTGTATGAGAAGGAAGAATAAGATGCCTGGCTTCCTCTGTGCCCGGGTTTACTCGGAAAGCTACATCTCCAGGCA
GACCAGTGAGACCGTCGAAAATGATAATGCATCGTCCTTTACCATGTAACACGAGAGCACAAAGCAACATTGCCCCAAAAGCCTTGGTGAAACTTGC
TATTACATATGAAAAAAAAAAAAAGCCATGCCCAAATATGTACAGTAACTATGGAAATTCAGCAAAGACTTCCTGCAAGTTCAGAAACAGCCATGAG
GTGGCACTATCAGCCAAATTCTTCCAGGTTGTTGGTTGACAAGAAACATTGCAGCTCCTCCCAGGTTTGGTTCTACAAAATAAGATGGGAAATGCCC
AGATTACTGGGTTTAGTTGCTTAATGAACATAAACATATTCCAGAAACGTTTCATGAAGGGGTTCACAGAACTAGTTGACCCCCTAACACCCCATAG
CCACAAAACAAGGATGTTACCTTGA

Mouse cDNA:

GGCTGCGAGAAGACGACAGAAGGGGGAGCACTGCTGGTTGTGTCTGTCAACAGAATAGTCCTCACATTCTTAGGACTGGAGCCTGGATAACCACTGA
GGCAGGAGTACCTGGCCAGTCTACTTTGGAGCTCAGCATTTTCTGGGGAATGAATTCCACAGAGTCCTACTTTGGAACGGATGATTATGACAACACA
GAGTATTATTCTATTCCTCCAGACCATGGGCCATGCTCCCTAGAAGAGGTCAGAAACTTCACCAAGGTATTTGTGCCAATTGCCTACTCCTTAATAT
GTGTCTTTGGCCTCCTGGGCAACATTATGGTGGTGATGACCTTTGCCTTCTACAAGAAAGCCAGATCCATGACTGACGTCTACCTGTTGAACATGGC
CATCACAGACATACTCTTTGTCCTCACCCTACCGTTCTGGGCAGTTACTCATGCCACCAACACTTGGGTTTTCAGCGATGCACTGTGTAAACTGATG
AAAGGCACATATGCGGTCAACTTTAACTGTGGGATGCTGCTCCTGGCCTGTATCAGCATGGACCGGTACATTGCCATCGTCCAGGCAACCAAATCTT
TCCGGGTACGCTCCAGAACACTGACGCACAGTAAGGTCATCTGTGTGGCAGTGTGGTTCATCTCCATCATCATCTCAAGCCCTACATTTATCTTCAA
CAAGAAATACGAGCTGCAGGATCGTGATGTCTGTGAGCCACGGTACAGGTCTGTCTCAGAGCCCATCACGTGGAAGCTGCTGGGTATGGGACTGGAG
CTGTTCTTTGGGTTCTTCACCCCTTTGCTGTTTATGGTGTTCTGCTATCTGTTCATTATCAAGACCTTGGTGCAGGCCCAGAACTCCAAGAGGCACA
GAGCCATCCGAGTCGTGATCGCTGTGGTTCTCGTGTTCCTGGCTTGTCAGATCCCTCACAACATGGTCCTCCTCGTGACTGCGGTCAACACGGGCAA
AGTGGGCCGGAGCTGCAGCACCGAGAAAGTCCTCGCCTACACCAGGAACGTGGCCGAGGTCCTGGCTTTCCTGCATTGCTGCCTCAACCCCGTGTTG
TATGCGTTTATTGGACAGAAATTCAGAAACTACTTCATGAAGATCATGAAGGATGTGTGGTGTATGAGAAGGAAGAATAAGATGCCTGGCTTCCTCT
GTGCCCGGGTTTACTCGGAAAGCTACATCTCCAGGCAGACCAGTGAGACCGTCGAAAATGATAATGCATCGTCCTTTACCATGTAACACGAGAGCAC
AAAGCAACATTGCCCCAAAAGCCTTGGTGAAACTTGCTATT

Figure 2 Comparison between human and mouse CCR6 amino acid sequences. Numbers at the right indicate the positions of the residues at the end of each line. Solid backgrounds indicate identities between the two proteins. Dots mark gaps introduced to create an optimal alignment. Tildes mark positions without corresponding residues. Putative transmembrane domains are indicated. The alignment was created using the PileUp and PrettyBox programs of the Wisconsin Sequence Analysis Package, Genetics Computer Group, Madison, WI.



predicted to contain 374 amino acids, with features that are typical for a member of the chemokine receptor subfamily of the seven transmembrane domain G protein-coupled receptor superfamily. These include an acidic N-terminal domain, a small and basic third intracellular loop, cysteine residues in the N-terminal domain (C36) and the third extracellular loop (C288), and a conserved DRY motif following the third transmembrane domain.

Relevant homologies and species differences

While obviously related to other chemokine receptors by sequence, CCR6 is not closely related to other receptors, showing greatest similarity to CCR7 (39% identity). Overall, human CCR6 is identical at 74% of its residues, as compared with mouse protein. As shown in Figure 2, mismatched residues are found disproportionately in the N-terminal region.

Affinity for ligand(s)

K_d for MIP-3α on CCR6-transfected cells is 0.1–12 nM (Baba *et al*., 1997; Greaves *et al*., 1997; Power *et al*., 1997) and on lymphocytes is 0.4 nM (Hieshima *et al*., 1997).

Cell types and tissues expressing the receptor

CCR6 mRNA is expressed in lymphoid tissue including spleen, lymph node, thymus, appendix, and peripheral blood lymphocytes (Zaballos *et al*., 1996; Liao *et al*., 1997c; Varona *et al*., 1998) and mRNA and protein are found in/on CD4+CD8+ T cells, dendritic cells derived from CD34+ bone marrow progenitors, and B cells (Zaballos *et al*., 1996; Baba *et al*., 1997; Greaves *et al*., 1997; Liao *et al*., 1997b, 1999; Power *et al*., 1997; Varona *et al*., 1998). On T cells, CCR6 is limited to those with a memory phenotype (Liao *et al*., 1999). CCR6 is found not only on freshly isolated peripheral blood T cells, but also on tumor-infiltrating lymphocytes that have been repeatedly activated *in vitro* (Liao *et al*., 1997a,b,c).

Regulation of receptor expression

Some investigators have reported induction of CCR6 mRNA on T cells after treatment with IL-2 (Baba *et al*., 1997), although others have reported down-regulation of mRNA after T cell activation with anti-CD3 and PMA (Greaves *et al*., 1997). Activation of T cells *in vitro* with anti-CD3 or IL-2 did not upregulate CCR6 surface expression (Liao *et al*., 1999) or responses to LARC/MIP-3α. Maturation of CD34+ progenitor-derived dendritic cells *in vitro* was

associated with downregulation of CCR6 mRNA and responses to LARC/MIP-3α (Dieu *et al*., 1998).

SIGNAL TRANSDUCTION

Cytoplasmic signaling cascades

Calcium signaling was blocked or diminished in tumor-infiltrating lymphocytes and in transfected cells by the addition of pertussis toxin, implicating $G\alpha_i$ proteins (Liao *et al*., 1997a; Power *et al*., 1997), and in transfected cells by inhibiting phospholipase C and depleting stores of intracellular calcium (Power *et al*., 1997).

BIOLOGICAL CONSEQUENCES OF ACTIVATING OR INHIBITING RECEPTOR AND PATHOPHYSIOLOGY

Unique biological effects of activating the receptors

CCR6 is unusual in that it is a receptor for an inflammation-induced chemokine that functions well on freshly isolated lymphocytes, i.e. on nonactivated cells, producing chemotaxis (Hieshima *et al*., 1997), calcium flux (Liao *et al*., 1997a), and rapid adherence to ICAM-1-coated glass under conditions of flow (Campbell *et al*., 1998). These activities were found on both CD4+ and CD8+ T cells, and were limited to T cells with a memory phenotype (Campbell *et al*., 1998; Liao *et al*., 1999). Consequently, CCR6 is the only chemokine receptor that functions well in the above assays specifically on nonactivated memory T cells. CCR6 is also unusual in being expressed and functional on a subset of immature dendritic cells and then being downregulated as the dendritic cells mature (Dieu *et al*., 1998).

References

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LICENSED PRODUCTS

Anti-human CCR6 mouse IgG_{2B} monoclonal antibody, clone 53103.111 from R&D Systems for flow cytometry.