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# Gene Section
## Review

# CCR9 (chemokine (C-C motif) receptor 9)

**Hisayuki Nomiyama, Osamu Yoshie**

Department of Biochemistry, Kumamoto University Medical School, Honjo, Kumamoto 860-0811, Japan (HN); Department of Microbiology, Kinki University School of Medicine, Osaka-Sayama, Osaka 589-8511, Japan (OY)

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## Identity

**Other names:** C-C CKR-9; CC-CKR-9; CCR-9; CDw199; Ckbeta-15; CMKBR9; GPR-9-6; GPR28

**HGNC (Hugo):** CCR9

**Location:** 3p21.31

**Note:** CCR9 is a G protein-coupled receptor with specifi-city for a CC chemokine CCL25 (originally described as thymus-expressed chemokine or TECK) and is one of the key molecules in leukocyte homing to gut mucosa.

## DNA/RNA

**Note**

The gene and mRNA for CCR9 are 16.6 and 2.7 kb in length, respectively.

### *Description*

The CCR9 gene consists of three exons, the second and third exons being the coding-exons. Alternative splicing of the gene generates two distinct mRNAs, CCR9-A and CCR9-B. The CCR9-A cDNA was the first to be cloned.

### *Transcription*

The CCR9-A mRNA is encoded by the three exons, while the CCR9-B lacks the sequence derived from the second exon of 49 bp. The CCR9 mRNAs are expressed predominantly in the thymus. Among the cell lines tested, T cell leukemia line MOLT-4 and HTLV-1+ T cells express CCR9 mRNA. The CCR9-A mRNA is expressed at ~10-fold higher levels than CCR9-B mRNA in the cells and cell lines investigated.

### *Pseudogene*

None.

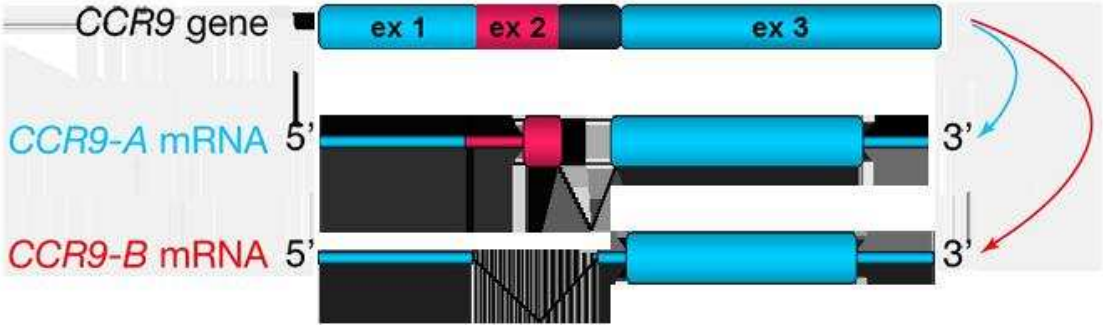
## Protein

**Note**

CCR9-A: 369 amino acids, 42015 Da.
CCR9-B: 357 amino acids, 40712 Da.

### *Description*

CCR9 is a member of the seven transmembrane G protein-coupled receptor superfamily, and is the single receptor for chemokine CCL25.




The CCR9 gene generates two distinct mRNAs.

### Expression

CCR9 is present on thymocytes as well as on intraepithelial and lamina propria lymphocytes of the small intestine. A small subset of lymphocytes in the colon is also expressing CCR9.

### Localisation

Cell membrane; Multi-pass membrane protein.

### Function

CCR9 mediates chemotaxis to CCL25, which is selectively expressed in the thymus and small intestine, and plays an important role in the recruitment of T cells into gut mucosa. Dendritic cells derived from gut-associated lymphoid tissues as well as retinoic acid have been shown to induce the expression of alpha4beta7 integrin and CCR9 on T cells, resulting in their preferential homing to the gut. Although CCR9 deletion in mice has no major effects on the intrathymic T-cell develop-ment, down-regulation of CCR9 on activated CD4+CD8+ double positive thymocytes has been shown to allow the migration of maturing thymo-cytes from the cortex to the medulla.
The EC50 of CCL25 for CCR9-A is somewhat lower than that for CCR9-B. CCR9-A-expressing cells are therefore more responsive to CCL25 than the cells expressing CCR9-B in chemotaxis and calcium influx experiments.

### Homology

CCR9 is closely related to the chemokine receptors CCR6, CCR7, and CXCR6.

## Implicated in

### T-cell acute lymphocytic leukemia (T-ALL)

**Oncogenesis**

Qiuping et al. (2003) assessed the expression of CCR9 in 21 T-ALL and 17 "T-cell chronic lymphocytic leukemia" (T-CLL) cases, and found that functionally active CCR9 was selectively and frequently expressed on T-ALL CD4+ T cells and was moderately expressed on T-CLL CD4+ T cells.
Annels et al. (2004) investigated homing receptor expression on the blast cells of 11 pediatric T-ALL patients. They found that CCR9 and CD103 (alphaE integrin) were expressed at high levels on T-ALL cells of one patient. This patient later switched to a clonally related acute myeloid leuke-mia during treatment, and the relapse of leukemia was confined to the gut. This study suggests a role of CCR9 in infiltration of leukemic cells into the gut.

### Adult T-cell leukemia (ATL)

**Oncogenesis**

ATL frequently invades the gastrointestinal tract. Nagakubo et al. (2007) examined CCR9 expression in five ATL-derived cell lines and 10 blood samples from ATL patients containing leukemic cells at high levels. Although all ATL cell lines were CCR9-positive, fresh ATL cells derived from patients were mostly negative. However, ATL cells became readily positive for CCR9 mRNA after one-day culture in parallel with the expression of Tax mRNA. This study suggests that CCR9 is inducible in ATL cells and may play a role in the high incidence of ATL cell invasion into the gastrointestinal tract.

### Melanoma metastasis to the small intestine

**Oncogenesis**

Letsch et al. (2004) assessed CCR9 expression in 20 melanoma cell lines. The CCR9-positive cell lines were established from metastases to small intestine (n = 3), lymph node (n = 4), and skin (n = 1). Only melanoma cell lines derived from small intestinal metastases, however, were responsive to CCL25. This study correlated functional expression of CCR9 with melanoma metastasis to the small intestine.
Amersi et al. (2008) assessed CCR9 expression in primary (n = 23) and metastatic (n = 198) melanomas, and melanoma lines derived from small intestinal metastases (n = 8). CCR9 expres-sion was observed in 88 of 102 metastatic melanomas from the small intestine, 8 of 8 mela-noma lines derived from small intestine metastasis, but none of 96 metastatic melanomas from other sites. In addition, 11 of 23 primary melanomas were CCR9-positive and 7 of these later developed small intestinal metastases. This study suggests that CCR9 has a role in melanoma metastasis to the small intestine.

### Melanoma metastasis

**Oncogenesis**

Seidl et al. (2007) investigated expression of eight chemokine receptors including CCR9 in 51 tissue samples of melanocytic origin. CCR9 mRNA was observed in more than half of the melanocytic lesions including lymph node metastases and visceral metastases. The authors concluded that there is no clear trend toward an association between the CCR9 expression levels and melanoma progression.

### Prostate cancer metastasis

**Oncogenesis**

Singh et al. (2004) investigated CCR9 expression in two prostate cancer cell lines. Both cell lines expressed CCR9. This study suggests that expres-sion and activation of CCR9 affect prostate cancer metastasis.

### Small intestinal Crohn's disease

**Oncogenesis**

Papadakis et al. (2001) found that CCR9+ T cells were markedly elevated in the peripheral blood of patients with Crohn's disease but not those with purely colonic

Crohn's disease. This study suggests selective involvement of CCR9 in the pathogenesis of small bowel Crohn's disease.

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