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**chemokine/chemokine receptor pair CCL20/CCR6 in human colorectal malignancy: An overview**

Frick VO *et al.* CCL20/CCR6 in colorectal cancer

Vilma Oliveira Frick, Claudia Rubie, Ulrich Keilholz, Pirus Ghadjar

**Vilma Oliveira Frick, Claudia Rubie,** Department of General-, Visceral-, Vascular- and Pediatric Surgery, University of the Saarland, Building 57, 66421 Homburg/Saar, Germany

**Ulrich Keilholz**, Charité Comprehensive Cancer Center, Charité Universitätsmedizin Berlin, Campus Charité Mitte, Charitéplatz 1, 10117 Berlin, Germany

**Pirus Ghadjar**, Department of Radiation Oncology, Charité Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany

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**Correspondence to:** **Vilma Oliveira Frick, PhD,** Department of General-, Visceral-, Vascular- and Paediatric Surgery, University of the Saarland, Building 57, 66421 Homburg/Saar, Germany. vilma.frick@uks.eu

**Telephone:** +49-6841-47867

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**Abstract**

Chemokines belong to a superfamily of small, cytokine-like proteins, which induce multiple physiological functions, particularly cytoskeletal rearrangement and compartment-specific migration through their interaction with G-protein-coupled receptors. Chemokines and their receptors have been widely acknowledged as essential and selective mediators in leukocyte migration in inflammatory response. It is now established that the chemokine/chemokine receptor system is also used by cancer cells to direct lymphatic and haematogenous spreading and additionally has an impact on the site of metastatic growth of different tumours. In recent years an increasing number of studies have drawn attention to CC-chemokine cysteine motif chemokine ligand 20 (CCL20) and its physiological sole receptor CCR6 to play a role in the onset, development and metastatic spread of various gastrointestinal cancer entities. Among various cancer types CCR6 was also demonstrated to be significantly overexpressed in colorectal cancer and stimulation by its physiological ligand CCL20 has been reported to promote colorectal cancer cell proliferation and migration *in vitro*. Further, the CCL20/CCR6 system apparently plays a role in the organ-selective liver metastasis of colorectal cancer. Here we review the literature on expression patterns of CCL20 and CCR6 and their physiological interactions as well as the currently presumed role of CCL20 and CCR6 in the formation of colorectal cancer and the development of liver metastasis, providing a potential basis for novel treatment strategies.

**Key words:** Chemokine/chemokine receptor pair**;** CCR6; CCL20; Colorectal cancer; Metastasis; Liver

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**Core tip:** Here we review the current literature published with respect to the expression pattern of chemokine/chemokine receptor pair cysteine motif chemokine ligand 20 (CCL20)/CCR6 and their physiological interactions as well as the currently presumed role of the CCL20/CCR6 system in the onset and development of colorectal cancer and its apparent role in the organ-selective metastatic spread of colorectal cancer cells to the liver. Disrupting the chemokine/chemokine receptor interaction of CCL20/CCR6 may therefore be a promising novel treatment strategy in colorectal cancer and metastasis.

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**INTRODUCTION**

Chemokines constitute a superfamily of small structurally related chemotactic cytokines that direct the migration of leukocytes throughout the body, both under physiological and inflammatory conditions[1,2]. Furthermore, they play a central role in many biological events, such as embryonic development, wound healing, angiogenesis, Th1/Th2 development, leukocyte homeostasis, lymphatic organ development, inflammatory diseases, tumour growth and metastasis. Chemokines exert their various biological functions by activating 7-transmembrane-domain G-protein coupled receptors on their target cells[3].

Since 1987, when CXCL8 (IL-8) was isolated as the first chemokine, remarkable progress was made in the field of chemokine research[4,5]. Until now, more than 50 different chemokines and 20 chemokine receptors have been discovered.

According to the presence and the relative position of the NH2-terminal Cystein (C) residues, chemokines are structurally grouped into the CC, CXC, CX3C and C chemokines. Alternatively, chemokines may be sub-divided according to their function into inflammatory/inducible or homeostatic/constitutive chemokines[2,6]. However, there are some members in the chemokine family which possess both inflammatory and homeostatic functions (Table 1).

To date, 20 different chemokine receptors have been characterized, which share many common structural features. They are composed of approximately 350 amino acids that are divided into a short and acidic N-terminal end, seven helical transmembrane domains with three intracellular and three extracellular hydrophilic loops and an intracellular C-terminus containing serine and threonine residues that act as phosphorylation sites during receptor regulation[7]. The interactions between chemokines and their receptors are often not perfectly specific. However, every chemokine receptor binds only one group of chemokines. Thus, on the basis of their binding-properties, chemokine receptors are divided into different families, CXC chemokine receptors, CC chemokine receptors, CX3C chemokine receptors and XC chemokine receptors that correspond to the four distinct subfamilies of the chemokines they bind.

While most chemokine receptors bind to multiple chemokines, providing a certain redundancy to the system. CCR6, however, is unique with respect to the fact that this receptor is found to bind only a single chemokine ligand, the homeostatic and inflammatory chemokine CCL20. The selectivity of the CCR6/CCL20 ligand receptor interaction in contrast to the other chemokine receptor binding properties already suggests tightly regulated functional roles.

**PHYSIOLOGICAL FUNCTIONS OF CCL20 AND CCR6**

The cysteine–cysteine motif chemokine ligand 20 (CCL20) – also known as liver-and activation-regulated chemokine (LARC), macrophage inflammatory protein-3a (MIP-3a), and exodus-1 – was discovered independently by three research groups using bioinformatic techniques[8-10].

CCL20 is expressed in a variety of human tissues and by different types of immune cells. While CCL20 expression was predominantly observed in mucosa associated lymphatic tissue (MALT), other lymphatic tissues, lung and liver tissues[9-11], its expression is virtually not detectable in spleen or bone marrow[12,13]. CCL20 expression has further been demonstrated in inflammation related cells such as endothelial cells[14,15], neutrophils[16], natural killer (NK) cells[17], Th17 cells[18], B-cells[19] and a variety of other immune cells[13,20] as well as in normal tissue of the colon, pancreas, stomach, prostate, testis, uterine cervix and skin[11].

The chemokine receptor CCR6 was originally described to be constitutively expressed in both lymphatic as well as in non-lymphatic tissue: predominantly in spleen, lymph nodes, appendix and pancreas and to a lesser extent in thymus, colon, small intestine, foetal liver and testis[11]. CCR6 is further expressed on various leukocyte subsets, including immature dendritic cells (iDCs), B-cells, T-cells (pro-inflammatory Th17 cells, regulatory Treg cells), NKT cells and neutrophils[11,21,22]. Early after its discovery, CCR6 was found to function in part as a key mediator linking iDCs to adaptive immune responses. In particular, it mediates the accurate positioning of iDCs in tissue[23], a critical early step in the afferent part of adaptive immune induction. As iDCs take up antigen, mature and become activated, they down-regulate CCR6 and up-regulate CCR7. This ‘chemokine receptor switch’ detaches the cell from tissue and enables its migration to draining lymph nodes in response to the CCR7 ligands CCL19 and CCL21 expressed on lymphatic endothelial cells[24,25]. To date, the exact role of the CCL20/CCR6 axis in steady-state immune dynamics still has to be elucidated. However, the fact that opposing cell subtypes like pro-inflammatory Th17 and regulatory Treg cells express and respond to CCL20 alludes to a potential regulatory balance between immune activation and suppression and implies an intriguing feedback loop[26].

Yamazaki *et al*[18] reported that lack of CCR6 in Th17 cells inhibits their own as well as Treg recruitment into inflammatory tissues, reasoning that CCR6 deficiency in T cells decreases the susceptibility to autoimmune diseases.

Among many other functions, the CCL20 and CCR6 system also plays an important and again tightly regulated physiological role in the colonic mucosa. Typically, CCL20 is weakly expressed in normal colonic mucosa. Yet, in response to an inflammatory stimulus CCL20 is strongly up-regulated. If mucosa cells grow in a polarized fashion, CCL20 secretion is located predominantly at the basolateral side of the cell and a pro-inflammatory stimulus through tumour necrosis factor alpha (TNF-α) or interleukin 1 beta (IL-1β) induces an increase in CCL20 secretion[27-29]. The chemokine/chemokine receptor pair CCL20/CCR6 presumably plays a role in combating infectious microorganisms, as chemoattraction of CCR6 bearing dendritic cells *via* CCL20 may contribute to the qualitative differences between systemic and mucosal immunity as shown *in vitro* and *in vivo* by Cook *et al*[30] and Kucharzik *et al*[31]*.* CCR6 expression is also found in the normal colon mucosa[32-35], but in contrast to CCL20, CCR6 expression is polarized predominantly to the apical side, thus, not accessible by CCL20 which is released from the basolateral side. Moreover, in contrast to CCL20 expression CCR6 expression is not influenced by inflammatory disease. The co-expression of ligand and receptor in the same cell opens up the possibility of autocrine and/or paracrine signalling, and consequently, as self-perpetuating cycle of recruitment within the intestinal epithelial cells[36].

**CCL20 AND CCR6 EXPRESSION IN CRC**

For clarity, the literature describing the CCL20 and CCR6 expression in colorectal cancer (CRC) is summarized in Table 2.

In sharp contrast to mucosa cells, CRC cells express both CCL20 and its corresponding receptor CCR6 in a non-polarized fashion, providing a basis for efficient autocrine and paracrine loops. Compared to the low CCR6 expression rates in normal colon mucosa tissue and normal liver tissue, CCR6 expression is significantly up-regulated in colorectal malignancies such as colorectal cancer[35-39] and colorectal liver metastasis[39,40]. Thus, Hu *et al*[38] described high expression rates of CCR6 in CRC which were significantly associated with metachronous metastasis to liver or lung. However, these high CCR6 expression rates were not organ-specific, thus allowing no differentiation between metastasis to liver or lung.

Accordingly, CCL20 expression in colorectal cancer[39-41] and colorectal liver metastasis[37,40] is also significantly increased compared to the corresponding normal tissue, respectively. Functional assays demonstrated that CCL20 stimulation of CRC cells led to increased proliferation and migration of CRC cells *in vitro* as well as to phosphorylation of p130cas, an adaptor/scaffolding protein associated with cytoskeletal and other focal adhesion proteins involved in adhesion and migration[32,33]. Moreover, stimulation with CCL20 led to activation of the ERK-MAP kinase and Act pathways[33]. To date, a large number of literature provides evidence that the expression of microRNAs (miRNAs) is dysregulated in cancer while it is yet unknown if this directly influences the carcinogenic process. In one of our studies we have outlined a functional interaction of miRNA-21 (miR-21) with the 3’UTR of CC-chemokine ligand CCL20. Further, we have demonstrated that miR-21 down-regulates CCL20 gene expression in three miR-21 transfected CRC cell lines, namely CaCo, SW480 and SW620[42].

A study performed by Dellacasagrande *et al*[43]demonstrated that small colorectal cancer liver metastases express higher amounts of CCR6 compared to the surrounding tissue hypothesizing a role for CCR6 in the development of liver metastasis. CCR6 expression was also shown to be lower in large established liver metastases compared to the corresponding primary CRC tumours, which could be due to the fact that CCR6 expression may not be necessary for colorectal cancer cells that have already formed large established metastases[33,34].

While the connection between inflammation and tumourigenesis is well established, the exact mechanisms linking these conditions have remained elusive. Successful evasion of the host´s immune response is thought to be the main mechanism responsible for cancer development[44]. Furthermore, communication between tumour cells and their microenvironment is widely thought to be crucial for tumour growth. Particularly, the interactions between tumour cells and infiltrating lymphocytes represent a powerful relationship that influences disease progression and patient prognosis[45]. Therefore, the types of tumour-infiltrating lymphocytes are believed to affect the prognosis of colorectal cancer[46]. Accumulating evidence indicates that although cancer patients exhibit a generalized immunosuppressive status, the inflammatory reaction at tumour site can foster tumour growth and progression. The perpetuation of chronic inflammation is largely achieved through positive feedback loops, which include inflammatory cells producing cytokines that induce chemokine synthesis in malignant and stromal cells leading to prolonged recruitment of inflammatory cells into the tumour environment[47]. The newly described interleukin-17 (IL-17) secreting subset of CD4+ T helper cells (Th17) are on of most critical immune cell subsets in this respect and thus have tumour-promoting effect. In patients with hepatocellular carcinoma[48], esophageal carcinoma[49], prostate cancer[50] and CRC[51] high levels of intratumoural Th17 cells were found to be positively associated with poor prognosis. Also it has been suggested by Liu *et al*[51] that the expression of IL-17 in Th17 cells and macrophages is involved in VEGF production and angiogenesis and is associated with poor survival in patients with colorectal carcinoma. Chen J *et al*[52] demonstrated that the distribution of helper T-lymphocytes is significantly different between colorectal tumour tissues and the peritumoural tissues. They reported that the percentage of infiltrating regulatory Th1 cells was significantly decreased, while the percentage of infiltrating suppressive Tregs-, Tr1 (type 1 regulatory T)-, and IL-17-positive cells were significantly increased in tumour tissues compared to peritumoural tissues. Likewise the ratio of suppressive T-helper (Tregs-, Tr1-, IL-17-postitive cells) to regulatory T-helper (Th1) cells was significantly higher in tumour tissues than in peritumoural tissues. It is well known, that the migration of T cells is tightly regulated by chemokine/chemokine receptor interaction[6]. Previous studies showed that recruitment of Th17 cells is governed by multiple pathways, including CCR2/CCL2, CCR4/CCL17/CCL22 and CCR6/CCL20[53-56]. In a recent study Yu *et al*[579] showed that the CCR6/CCL20 pathway is the preferential chemoattractant for the trafficking of circulating Th17 cells into tumour tissue of cervical cancer.

Chin *et al*[58]demonstrated *in vitro* that IL-17 treatment induces an increase of CCR6 expression in colorectal cancer HCT-116 cells and that IL-17 induced cell migration is mediated through the ERK and p38 intracellular cascades and through the transcription factor NF-κB.

It is also accepted that tumour-associated macrophages (TAMs) contribute to the increased production of CCL20 that recruits CCR6+ regulatory Tregs cells and promotes CRC in mice[59]. Another study demonstrated in a CCR6 mice knock out model that intestinal tumourigenesis driven by CCL20/CCR6 interactions may be driven by macrophage recruitment into the intestine as well as proliferation of neoplastic epithelial cells[39].

It is also well known that immune cell subsets, when chronically activated, directly foster tumour development and promote cancer progression[60,61]. Kryczek *et al*[62] focused on the interaction between IL-22 secreting (IL-22+) immune cells and cancer (stem) cells. They demonstrated that IL-22+ CD4+ T cells promote colorectal cancer stemness *via* STAT3 transkription factor activation and induction of the methyltransferase DOT1L and that is relevant for outcome in patients with CRC.

**CCL20 AND CCR6 IN TUMOUR METASTASIS**

The morbidity and mortality of patients with cancer is mainly attributed to distant tumour metastasis[63]. For instance, the 5-year survival rate for patients with tumours restricted only to the colon decreases dramatically from 90% to 10% in the presence of distant metastasis[64,65]. The current understanding of the metastatic process is far from sufficient, but various experimental and clinical findings support the thesis that metastatic dissemination is a result of a complex multistep molecular machinery which does not occur randomly, but as a result of different coordinated organ-specific processes[66]. Thus, some organs, such as liver, lung, brain and bones are frequently involved in tumour metastasis, while other organs like muscle and mucosal membranes of the gastrointestinal tract are seldomly affected by metastasis. Such differences cannot solely be explained by anatomic differences in blood and lymphatic supply.

In the last decades different concepts were postulated trying to explain the metastatic behaviour of different tumour entities. The most central of these theories is the ‘seed and soil’ theory of metastasis, first proposed in 1889 by Stephen Paget[67]. Paget predicted that cancer cells (the ‘seed’) can survive and proliferate only in secondary sites (the ‘soil’) that produce growth factors appropriate to that type of cell, and this theory has largely withstood the test of time[68].According to the ‘adhesion theory’ cancer cell extravasation is triggered by certain adhesion molecules that are expressed on endothelial cells in an organ specific manner[69]. Another theory gaining popularity in recent years suggests that epithelial-mesenchymal transition (EMT) may contribute to the metastatic process. The EMT phenotype in cancer has been associated with a decrease in tumour growth, increased resistance to apoptosis, increased motility and invasiveness and enhanced metastatic ability[70]. As these phenotypic transitions are reversible it is hypothesized that tumour cells may transform back into an epithelial phenotype once they have reached their destination thus facilitating tumour growth in the secondary site[71].

The ‘homing theory’ proposes that different organs produce chemotactic factors which can attract the corresponding chemokine receptor bearing cancers cells so that they migrate into distinct organs towards the chemokine gradient[72-74]. Thus, various publications support the involvement of chemokine/chemokine receptor interactions in tumourmetastasis[75-81] and demonstrated that blockade of the respective chemokine/chemokine receptor interaction leads to a reduction of metastasis development *in vivo*[82-84].

Colorectal cancer is a tumour with a high propensity for metastatic spread, mostly affecting liver and lungs. Liver metastases develop in approximately 50% of CRC patients at some point in the course of their disease and worsen the prognosis for patient survival dramatically[64]. With respect to colorectal liver metastasis CCR6 is of special importance as well as its unique chemokine ligand CCL20, which is predominantly expressed in mucosa-associated and lymphoid tissues and in the liver[11]. Within the liver, the CCL20 expression profile is not random, but predominantly limited to the periportal area. Such local designation may be explained by the fact, that the periportal area is the physiological entry site of the blood draining from most of the lower gastrointestinal tract. Also potential invading microorganisms are likely to use this mode of entry. Therefore, the periportal expression of CCL20 may be important for recruiting CCR6-expressing dendritic cells as a response to encounter with microorganisms. In addition, the periportal area is also the presumed initial entry site for cancer cells, which originate from cancers of the colon or proximal rectum, which have gained access to the portal bloodstream[10,11,20].

Recent studied explored the question, if there was any physiological example of CCL20/CCR6 interaction resulting in recruitment of CCR6-expressing cells to the liver. Indeed, CCL20 is weakly expressed in normal liver, but after an inflammatory stimulus CCL20 is strongly up-regulated and this results in the chemo-attraction of CCR6 bearing T-lymphocytes into the liver *in vitro* and *in vivo*[20,85].

If you assemble all these pieces of evidence, you may hypothesize, that the expression of CCL20 within the periportal area of the liver may be ‘the soil’ for CCR6 expressing CRC cells, which detached from the primary tumour, ‘the seed’. If micrometastases are present, the autocrine mechanism of CCL20/CCR6 interactions might contribute to enhanced tumour growth. On the other hand, the tumour itself may provide support for tumour growth in a paracrine manner by triggering CCL20 production in the surrounding liver tissue.

Two independent studies performed by Ghadjar *et al*[34] and Hu *et al*[38] demonstrated in concordance with the hypothesis stated above that increased CCR6 expression on primary colorectal cancers are an independent risk factor for distant metastasis. Furthermore, multivariate analysis showed that along with the expression of CCR6 also CXCR2 expression and the preoperative serum carcinoembryonic antigen (CEA) level were the major independent factors affecting distant metastasis[38].

Moreover, Ghadjar *et al*[34] demonstrated a significant up-regulation of CCR6 in colorectal cancer compared to the colonic mucosa. Interestingly, the CCR6 expression in liver metastatic tissue was significantly down-regulated as compared to the primary tumour. In a parallel study, we were able to confirm the finding by Ghadjar *et al*[35] namely the up-regulation of CCR6 from colonic mucosa to colorectal cancer. Further, we could demonstrate that patients with CRC who experienced liver metastasis, express significantly higher amounts of CCL20 in their liver compared to controls without metastases, suggesting an association between CCL20/CCR6 expression in human CRC and the promotion of colorectal liver metastasis. Moreover we demonstrated that CCL20 expression correlates clinicopathologically with the transition of an inflammatory disease to the adenoma and adenocarcinoma sequence. Likely, serum CCL20 was recently suggested as an independent predictive factor for liver metastasis correlating high levels of serum CCL20 with poor prognosis[86].

Taken together, these data strongly support the hypothesis that up-regulation of CCR6 expression and high amounts of CCL20 in the organ of metastatic spread, are correlated with liver metastasis, suggesting that the chemokine/chemokine receptor CCL20/CCR6 system plays a central role in tumour progression and metastasis.

However, this hypothesis needs to be further validated by functional studies.

The identification of key targets promoting metastasis is important for the development of new treatments and inhibiting metastasis development by interfering with the chemokine/chemokine receptor is a promising strategy for adjuvant treatments[87,88].

Moreover, it would be important to investigate if a neutralizing antibody against CCR6 can block the influence of CCL20 on proliferation and migration *in vitro*. Subsequently, the concept of liver metastasis facilitated by CCL20/CCR6 interactions should also be validated *in vivo* by knock-out animal models.

**CONCLUSION**

The chemokine/chemokine receptor pair CCL20/CCR6 is involved in colorectal cancer leading to proliferation and migration *via* autocrine and/or paracrine mechanisms. Moreover, the formation of colorectal liver metastasis might be advantaged by CCL20/CCR6 interactions.

The identification of key targets promoting disease progression and metastasis is of great interest for the development of specific treatment strategies. Attempts to inhibit metastasis by interfering with chemokine/chemokine receptor interactions is a promising new therapeutic strategy. Various small-molecule chemokine receptor antagonists compounds are currently undergoing development in phase I to III studies in infectious and autoimmune diseases and more recently also in cancer.

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| **Table 1 Nomenclature of selected chemokines, coding chromosomal location, major function and interacting receptor** |
|  | **Synonymes** | **Location** | **Major Function** | **Receptor** |
| CC Chemokine |  |  |  |  |
| CCL3 | MIP-1α/LD78α | 17q11.2 | Inflammation | CCR1 |
| CCL4 | MIP-1β | 17q12 | Inflammation | CCR1CCR5 |
| CCL5 | RANTES | 17q12 | Inflammation | CCR5 |
| CCL19 | MIP-3β/ELC/Exodus-3 | 9p13.3 | Homing | CCR7 |
| CCL20 | MIP-3α/LARC/Exodus-1 | 2q36.3 | Homing, Inflammation | CCR6 |
| CCL21 | 6Ckine/SLC/Exodus-2 | 9p13.3 | Homing | CCR7 |
| CCL25 | TECK/Ckβ15 | 19p13.2 | Homing | CCR9 |
| CXC Chemokine |  |  |  |  |
| CXCL8 | IL-8 | 4q13.3 | Inflammation, Angiogenesis1 | CXCR1CXCR2 |
| CXCL9 | MIG | 4q21.1 | Inflammation,Angiogenesis2 | CXCR3 |
| CXCL10 | IP-10 | 4q21.1 | Inflammation,Angiogenesis2 | CXCR3 |
| CXCL11 | I-TAC | 4q21.1 | Inflammation,Angiogenesis2 | CXCR3CXCR7 |
| CXCL12 | SDF-1α/β | 10q11.21 | Homing | CXCR4CXCR7 |
| CXCL13 | BLC/BCA-1 | 4q21.1 | Homing | CXCR5 |
| CX3C Chemokine |  |  |  |  |
| CX3CL1 | Fractalkine | 16q13 | Inflammation | CX3CR1 |
| C-Chemokine |  |  |  |  |
| XCL1 | Lymphotactin/SCM-1α | 1q24.2 | Homing | XCR1 |
| XCL2 | SCM-1β | 1q24.2 | Homing | XCR1 |

1 Promotor of angiogenesis; 2 Inhibitor of angiogenesis.

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| --- |
| **Table 2 CCL20 and CCR6 data in colorectal cancer available in the literature** |
| **Author** | **Year** | **Cell-****lines** | **Clinical samples** | **Animal****model** | **CCL20 determination** | **CCR6****determination** | **Functional****assays** | **Reference** |
| Rossi | 1997 | Yes | No | No | SB, NB | no | No | 8 |
| Izadpanah | 2001 | Yes | Yes | No | IHC, PCR, ELISA | IHC, PCR | No | 27 |
| Fujiie | 2001 | Yes | No | No | ELISA, PCR | no | No | 28 |
| Kwon | 2002 | Yes | No | No | ELISA, PCR | no | No | 29 |
| Dellacasagrande | 2003 | No | Yes | Yes | No | PCR | AA | 43 |
| Yang | 2005 | Yes | No | No | No | FC, CM | cAMP, PP, CF | 32 |
| Brand | 2006 | Yes | Yes | No | PCR, IHC | PCR, IHC | PA, WA, APA | 33 |
| Ghadjar | 2006 | No | Yes | No | No | IHC | No | 34 |
| Rubie | 2006 | No | Yes | No | PCR, ELISA | PCR, WB | No | 35 |
| Liu  | 2011 | Yes | No | Yes | IF, WB, PCR | FC, IF | No | 51 |
| Vicinus | 2012 | Yes | No | No | PCR, ELISA |  | miR, LUC | 42 |
| Hu | 2013 | No | Yes | No | No | IHC | No | 38 |
| Frick | 2013 | No | Yes | No | PCR, ELISA, IHC | PCR, IHC | No | 37 |
| Vicinus | 2013 | No | Yes | No | PCR, ELISA, IHC | No | No | 41 |
| Nandi | 2014 | Yes | Yes | Yes | ELISA, IHC | IHC, PCR, WB | No | 39 |

SB: Southern blot; NB: Northern blot; PCR: Polymerase chain reaction; IHC: Immunohistochemistry; PA: Proliferation assay; ELISA: Enzyme-linked immunosorbent assay; AA: Actin assay; FC: Flow-cytometry; CM: Confocal microscopy; cAMP: cAMP assay; PP: Protein phosphorylation; CF: Calcium flux; WA: Wounding assay; APA: Apoptosis assay; WB: Western blot; IF: Immunofluorescece staining; miR: miRNA assay; LUC: Dual luciferase reporter assay.