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EXPRESSION OF CHEMOKINE (C-C MOTIF) RECEPTOR 7 IN PROSTATE CANCER TISSUE OF YOUNG PATIENTS AND IN METASTATIC CANCER CELLS

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***Background*: Chemokine (C-C motif) receptor 7 (CCR7) is a chemokine receptor involved in the carcinogenesis of several types of tumors due to its promoting action in epithelial-mesenchymal transition events, invasion, angiogenesis and metastasis. However, its role in prostate cancer (PCa) remains unclear. *Aim*: To evaluate CCR7 expression by immunohistochemistry in prostate tumors from young patients and to determine the possible relationship with the clinicopathological characteristics. *Materials and Methods*: We analyzed retrospectively paraffin-embedded tissue sections from 23 young PCa (⩽ 55 years old) patients and evaluated the transcriptomic expression in the TCGA database. *Results*: Expression of CCR7 was observed in 15 cases (65%). The tissue samples from younger patients (⩽ 50 years) were mostly positive in 72.7% (8/11) of cases. High grade GS (⩾ 3) tumors were CCR7-positive in 71% cases. The malignant cells present in lymph nodes were CCR7 positive in 100% cases. The bioinformatic analysis showed a high CCR7 expression associated with the presence of metastasis (FC = 2.6, $p = 0.03$) in the Cancer Genome Atlas (TCGA) PCa cohort (PRAD). *Conclusion*: We showed that CCR7 expression in tumors from young patients is associated with the early onset of the disease and could also be related to lymph node metastasis.**

***Key Words*: CCR-7, chemokine, prostate cancer, early onset.**

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Prostate cancer (PCa) is the most common tumor in men and the fifth most common cause of cancer death worldwide. It is estimated that there were almost 1.4 million new cases of PCa and 375,304 associated deaths worldwide in 2020 [1]. Early-onset PCa (EO-PCa) has been defined as PCa in young patients under 50 years of age at the time of PCa diagnosis [2, 3] However, other studies have set the age limit at 60, 55 and 45 years of age [2]. Several risk factors are associated with EO-PCa, such as family medical background, ethnicity and genetic factors like single nucleotide polymorphisms and mutations in BRCA1, BRCA2, HOXB13, MSH2, ERCC2 and CHEK2_non1100del [4–7] genes, as well as rearrangements of genes in the androgen receptor axis (e.g., TMPRSS2-ERG, PTEN and AR) [8].

Several hallmarks have been described that identify changes in the activity, function, morphology and behavior of the cancer cells, and which explain their admirable ability to bypass the cellular, tissue and systemic control of the organisms in which the cancer is established. One of the cancer hallmarks is to promote inflammatory events in their environment [9], which are characterized by the recruitment of leukocytes, production of cytokines and chemokines, induction of angiogenesis, presence of epithelial-mesenchymal transition events (EMT), and the promotion of migration and metastasis [10, 11]. Several immune cells and chemokines influence PCa progression through action on the molecular pathways stimulating proliferation, angiogenesis, migration, invasion and metastasis events [11]. In EO-PCa, Ding *et al.* [12] detected abnormal expression of genes involved in inflammatory and antitumor immune-related pathways (CTL4, IDO1/TDO2). In a previous study, we found dysregulated expression of mRNAs associated with inflammatory pathways in young PCa patients [13, 14].

Chemokines are chemotactic cytokines that act by binding to their respective receptors. In cancer, some chemokines and their receptors have a promoting role in carcinogenesis, inflammation, immune surveillance and cancer progression events [10, 11]. One of these chemokine receptors is chemokine (C-C motif) receptor 7 (CCR7) which, along with its ligands CCL19 and CCL21, acts in the trafficking and homing of T cells, B cells, natural killer cells and mature dendritic cells [15]. CCR7 is a G protein-coupled receptor and it has been demonstrated that the complexes CCR7-CCL21/CCL19 are involved in the promotion of EMT, invasion, angiogenesis and metastasis events in several types of tumors, such as breast, lung, pancreatic and esophageal, among others [16]. CCR7 expression often correlates with lymphatic metastases and poor prognosis [17]. A meta-analysis showed that higher expression of CCR7 in different cancers is correlated with

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Abbreviations used: CCR7 – chemokine (C-C motif) receptor 7; EMT – epithelial-mesenchymal transition; EO-PCa – early-onset PCa; FC – fold change; FDR – false discovery rate; GS – Gleason score; H&E – hematoxylin and eosin; HIF – hypoxia inducible factor; MAPK – mitogen activated protein kinase; MMP – matrix metalloproteinase; PCa – prostate cancer; TCGA – The Cancer Genome Atlas.

poorer overall survival and progression-free survival [18]. CCR7 and its ligands have also been proposed as targets for therapeutic intervention due to their role in carcinogenesis [17].

Few studies have evaluated the role of CCR7-CCL21/CCL19 in PCa. It has been observed that CCR7 is associated with EMT, invasion, metastasis [19, 20] and enzalutamide resistance [21]. The goal of this study was to evaluate the expression of CCR7 in young PCa patients and its possible relationship with the clinicopathological characteristics.

MATERIALS AND METHODS

Patient samples. Formalin-fixed, paraffin-embedded tissue samples from young PCa patients (age ⩽ 55) were retrieved from the surgical archives of the Laboratory of Pathology, National Cancer Institute, Bogotá, Colombia. The samples included were obtained between 2007 to 2014. Hematoxylin and eosin (H&E) stained slides were reviewed to confirm the diagnosis. The clinicopathological features were collected, including Gleason score (GS), extraprostatic extension, margins, seminal vesicle, perineural invasion, lymphatic invasion and AJCC prostate cancer stage group 2018.

Immunohistochemical study. 3 μm tumor tissue sections were kept at 60 °C for 2 h, dewaxed by incubation with xylol for 10 min and rehydrated with ethanol of different grades. Heat-mediated antigen recovery was performed with EDTA 10X (Lab Vision) at a 1/10 dilution in a "vaporizer" for 50 min. Next, the slides were immersed in a 1/10 hydrogen peroxide solution (UltraVision Hydrogen Peroxide Block) for 10 min at RT. Afterwards, they were incubated with primary Anti-CCR7 (ab 32527; Abcam) at a 1/1000 dilution for 2 h at RT in a wet chamber, before washing twice with Tris-buffered saline 1/10 (Dako, pH 7.6). Later, the slides were incubated with biotinylated secondary antibody (Primary Antibody Amplifier) for 10 min at RT. They were subsequently buffered with diaminobenzidine and counterstained with hematoxylin for 2 min. Negative controls were performed by omission of the primary antibody. Positive control slides included sections of tonsil.

CCR7-positive staining was assessed by a single pathologist who was blinded to their clinical features. The staining pattern was assessed as positive cytoplasmic or membranous in malignant cells. The intensity was classified as weak (+), moderate (++) or strong (+++).

RNA expression bioinformatics analysis. The data obtained from The Cancer Genome Atlas (TCGA) and processed by recount2 [22] were used for data analysis. Gene counts for all PCa cases were downloaded. The data in recount2 were processed with Rail-RNA [22]. Quality control with density plots and box plots was performed to identify that the selected samples had a similar distribution before and after normalization. Additionally, a multidimensional plot was performed to identify outlier samples.

Identification of differentially expressed genes. The gene count data of the mRNA were analyzed on the Galaxy web platform [23]. The data were normalized by library sizes using the trimmed mean of M-values method. Genes without more than 1 count per million mapped reads in at least 50% of the samples were considered not expressed and were filtered out. The limma-voom method was used to identify the differentially expressed genes.

With the TCGA transcriptomics data, three different comparisons were performed to identify the relevance of CCR7 expression in the molecular biology of PCa. Firstly, the transcriptome of the tumor tissue from young people (83 samples, < 55 years old) was compared against the transcriptome of normal tissue from people in the same age range (10 samples). Secondly, the transcriptome of tumors from older individuals (49 samples, > 65 years old) was compared against the transcriptome of normal tissue from people in the same age range (14 samples). Thirdly, the transcriptome of tumor tissue samples from people of any age with metastasis (79 samples) was compared against tumor tissue obtained from individuals of any age without metastasis (367 samples). Finally, fold change (FC) and false discovery rate (FDR) values for CCR7 were extracted for all three analyses. A priori, it was defined that a gene is differentially expressed if the linear FC is higher than the absolute value of 1.5 and the FDR is lower than 0.05.

Statistical analysis. Univariate analysis was applied to determine distribution of clinical and pathological findings. Chi-square test and Mann — Whitney test were employed to determine statistically significant differences between CCR7 and clinical and pathological findings. $p < 0.05$ was considered statistically significant. Statistical analysis was performed with the STATA 13.

RESULTS

A total of 23 samples of young PCa patients were included (20 prostatectomy samples and 3 biopsies). The demographic characteristics of our study population are summarized in the Table. The median age of the patients was 50.8 years (range 46–55); their GS and AJCC PCa staging are shown in the Table. Four patients were of N1 status. The prostatectomies and the biopsies were done in the National Cancer Institute, Bogotá, Colombia. Only two patients (GS 3) received a treatment before prostatectomy (one patient with radiotherapy and the other with leuprolide and bicalutamide).

The expression of CCR7 in malignant cells was observed in 15 cases (65%). The median age was 50.3 years *vs* 51.6 years in CCR7 negative samples (n = 8), as tumor tissue of younger (⩽ 50 years old) patients was mostly positive for CCR7 staining (8/11; 72.7%). 12 cases had weak (+) intensity and three moderate (++) intensity. High grade GS (⩾ 3) tumors were CCR7-positive in 71% cases. Among the four patients with compromised lymph nodes, CCR7 was positive in all cases. The malignant cells were positive in the prostate and lymph nodes, two of which had moderate intensity in the prostate and the lymph nodes (the Figure).

In the analysis of the TCGA database, we did not find differences among the CCR7 mRNA expression of tumor tissue *vs* normal tissue in young patients (< 55 years old) (FC = 0.21, $p = 0.66$), while in old patients (> 65 years old) we observed differences (FC = –0.88, $p = 0.01$) with lower

Table. Clinicopathological features of PCa patients included in this study

Variable	CCR7 positive (n = 15)	CCR7 negative (n = 8)	Total (n = 23)	*p*
Age, median (years) (range)	50.3 (46–55)	51.6 (49–54)	50.8 (46–55)	0.31
PSA (ng/mL) before treatment	8.86 (2.73–99)	7.3 (4.3–39.2)	8.32 (2.73–99)	0.31
GS group				0.35
1	4	5	9	
2	6	1	7	
3	2	2	4	
4	2	0	2	
5	1	0	1	
AJCC PCa stage				0.24
IIA	0	1	1	
IIB	7	5	12	
III	4	2	6	
IV	4	0	4	
Nodal stage				0.25
N0	0	0	0	
N1	4	0	4	

expression in tumor tissue. In addition, we observed that high CCR7 expression was associated with the presence of metastasis (FC = 2.6, $p = 0.03$) in the TCGA PCa cohort (PRAD).

DISCUSSION

In the present study, we observed CCR7 expression in 15 of 23 malignant prostate gland cells and in 100% (4/4) of the metastatic cases, suggesting that CCR7 is involved in the carcinogenesis of younger PCa patients. The upregulation (FDR 2.3) of CCR7 in young PCa patients was observed by Ding *et al.* [12] in a molecular study which included 49 PCa patients, 24 of them young (38–45 years old) and 25 old (71–74), with the same GS of 7 (3+4) and with T2a and T2c by the pathological stage. The PSA range was 1.9–15.4 ng/mL and the samples included different ethnic groups, comprising 88% whites, 4% african americans, 4% hispanics and 4% asians. They found that CCR7 and its ligands (CCL21 and CCL19) were age-related differentially expressed genes and they are involved in the inflammatory and immune related pathways. Also, it was observed in the molecular analysis that CCR7 is a target of several genes upregulated in younger PCa patients. In addition, Ding *et al.* [12] and our previous study [13] found that mRNA hubs such as hsa-miR-142-5p, hsa-miR-150-5p and hsa-miR-146b-3p were correlated with CCR7 expression.

Both immunohistochemical study and bioinformatic analysis showed that CCR7 was present in PCa cells and non-tumor cells of the prostate. Ding *et al*. [12] also found the similar result. One explanation is that tumor-induced inflammation cannot be successfully resolved because it is persistent chronic inflammation [12, 24]. It is interesting that in the RNA expression results, in the PCa patients over 65 years, a loss of CCR7 expression in malignant cells was observed compared to non-tumor cells (FC = –0.88, $p = 0.01$).

In our analysis, we observed that expression of CCR7 is associated with metastasis (FC = 2.6, $p = 0.03$) and it was observed in metastatic malignant cells through immunohistochemistry (the Figure). The mechanisms related to CCR7 expression and metastasis are not fully understood. Studies have shown that CCR7 could be activated not only by pro-inflammatory mediators but also by other signalling pathways as well. It has been proposed that CCR7 is associated with complex chemokine–chemokine receptor interaction in the microenvironment and is involved in several steps during the process of metastasis (arrest, dissemination, extravasation, survival/proliferation) under the control of the immune system trafficking to the site of inflammation [25]. CCR7 affects tumor vascularization by increasing expression of vascular endothelial growth factors (VEGF-A, VEGF-C, VEGF-D), which leads to angiogenesis and lymphangiogenesis [16].

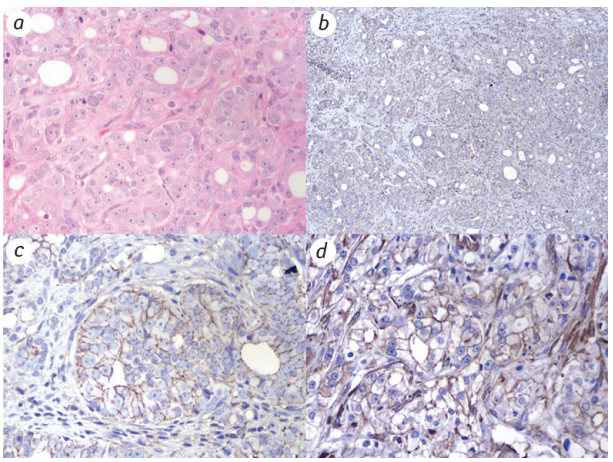

Figure. GS 4 PCa: *a* — H&E staining (×40); *b* — CCR7 protein expression in malignant cells in prostate (+) (×10); *c* — CCR7 protein expression in metastatic malignant cells in lymph node (+) (×40); *d* — CCR7 protein expression in metastatic malignant cells in lymph node (++) (×40)

In PCa cells, it has been observed that the expression of CCR7 is involved in their invasion and metastasis. Maolake *et al*. [20] found that TNF-α leads to the induction of CCR7 expression and the CCL21/CCR7 axis, which might increase migration to lymph nodes. Du *et al*. [19] observed that upregulation of Notch1 by CCR7 can be associated with EMT and participate in invasion and metastasis by activating mitogen activated protein kinase (MAPK) and NF-κB signaling pathways [19]. Bao-Jin *et al*. [26], on the other hand, detected that the silencing of CCR7 inhibits the growth, invasion and migration of PCa cells induced by VEGF-C and also this silencing may inhibit matrix metalloproteinase (MMP)-2 and MMP-9 protein expression. Finally, Youlin *et al*. [27] found that CCR7, along with MMP-9 and Notch1, can be increased by prostaglandin E2, a known member involved in immune responses inducing dendritic cell migration and homing to draining lymph nodes.

Chemokine receptors such as CCR7 activate intracellular signaling pathways in tumor cells like PI3K/Akt, Jak/STAT and MAPK/ERK [17]. As shown before, CCR7 may induce growth, invasion and migration of PCa cells through the MAPK pathway [19, 26, 27]. MAPKs comprise a family of protein-serine/threonine kinases that are involved in the different cellular processes, such as cell proliferation, survival, death, differentiation, and transformation [28]. In PCa, the MAPK pathway is involved in apoptosis, survival, metastatic potential and androgen-independent growth of PCa [28]. Interestingly, we previously observed that the MAPK pathway is more overrepresented in younger PCa patients than in older PCa patients (71–74 years old) [13]. Our previous study also found that mRNA hubs such as hsa-miR-142-5p, hsa-miR-150-5p and hsa-miR-146b-3p were overexpressed in younger PCa patients and these mRNA hubs were correlated with CCR7 expression, and hsa-miR-142-5p and hsa-miR-146b-3p were also correlated with MMP-9 expression [13]. MMP-9 is involved in proliferation, angiogenesis, EMT, apoptosis and metastasis of PCa [29]. As shown by Bao-Jin *et al*. [26] and Youlin *et al*. [27], CCR7 interacts with MMP-9 and this may be related to the growth, invasion and migration of PCa cells.

Moreover, hypoxia is a common phenomenon in human solid tumors and is related to the promotion of angiogenesis, invasion and metastasis [30]. In PCa, hypoxia promoted EMT, invasion, metastasis and resistance to radiotherapy and chemotherapy [31–34]. The key regulator under hypoxic conditions is hypoxia inducible factor-1 (HIF-1) alpha that was observed upregulated in the early stage of PCa and subsequent down-regulation at later metastatic stages [34]. In PCa, it was also observed that the hypoxia increases CX3CR1 expression via HIF-1 and NFκB [35]. It has been observed that hypoxia induces CCR7 expression via HIF-1 alpha and HIF-2 alpha in different tumors such as cancer of breast [36], lung [37], head and neck [38] and ovary [39]. This interaction among hypoxia-HIF1alpha-HIF2alpha-CCR7 was associated with migration and invasion [37, 38]. This axis also was associated with the expression of pERK1/2, a member of MAPK/ERK pathway [37].

The major limitation of this study is the small number of young PCa patients; therefore, additional studies in larger cohorts are needed to establish a relationship linking CCR7 expression with carcinogenesis and metastasis in PCa.

In the present study, we provide information that the youngest PCa patients had higher CCR7 positivity in primary tumors suggesting that CCR7 is involved in the early onset of the disease. In addition, we found that CCR7 expression was correlated with lymph node metastasis. Taken together, the previous studies support our findings and suggest that CCR7 may participate in the PCa metastasis, especially in early-onset of the disease.

ETHICS APPROVAL

This study was approved by the Research Ethics Board at the Instituto Nacional de Cancerología, E.S.E., Bogotá-Colombia, and it was designated as an exempt study for informed consent.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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ЕКСПРЕСІЯ ХЕМОКІНОВОГО (С-С МОТИВ) РЕЦЕПТОРА 7 (CCR7) В КЛІТИНАХ ЗЛОЯКІСНИХ ПУХЛИН ПЕРЕДМІХУРОВОЇ ЗАЛОЗИ ТА В МЕТАСТАЗАХ У ХВОРИХ МОЛОДОГО ВІКУ

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Стан питання: Згідно з даними літератури, хемокіновий (С-С мотив) рецептор 7 (chemokine (C-C motif) receptor 7 — CCR7) бере участь у виникненні та прогресії кількох типів раку шляхом регуляції епітеліально-мезенхімального переходу, механізмів інвазії, ангіогенезу та метастазування. Однак роль цього рецептора у виникненні та прогресії раку передміхурової залози (РПЗ) залишається невивченою. Метою роботи було оцінити експресію CCR7 в пухлинній тканині хворих та визначити можливий зв'язок з клініко-патологічними характеристиками РПЗ хворих молодого віку. ***Матеріали та методи:*** Дослідження проведено на зразках пухлинної тканини 23 хворих на РПЗ (⩽55 років) ретроспективної групи, які знаходилися на лікуванні в Національному інституті раку, Богота, Колумбія. Визначення експресії CCR7 в пухлинній тканині проводили імуногістохімічним методом. Аналіз експресії CCR7 на транскриптомному рівні проведено з використанням бази даних TCGA. ***Результати:*** У ході аналізу результатів імуногістохімічного дослідження було встановлено наявність експресії CCR7 у 65,0% хворих на РПЗ. Продемонстровано наявність експресії у 72,7% пацієнтів з РПЗ молодого віку (⩽ 50 років), новоутворення яких характеризувалися низьким ступенем диференціювання 71% (високий бал за Глісоном). Експресію CCR7 виявлено у 100% зразків пухлинної тканини метастазів у реґіонарні лімфатичні вузли. Біоінформатичний аналіз, проведений з використанням бази даних TCGA, підтвердив наявність асоціативних зв'язків між високим рівнем експресії та наявністю метастазів (FC = 2,6, p = 0,03) у хворих на РПЗ. ***Висновки:*** Показано, що експресія CCR7 в пухлинній тканині хворих на РПЗ молодого віку асоціюється з раннім початком захворювання, а також може бути пов'язана з метастазуванням у лімфатичні вузли.

Ключові слова: CCR-7, хемокін, рак передміхурової залози, ранній початок захворювання.