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КЛІНІЧНА ЕНДОКРИНОЛОГІЯ

LEVEL OF MONOCYTE CHEMOATTRACTANT PROTEIN-1 IN MEDULLARY AND PAPILLARY THYROID CARCINOMAS*

N. Ya. Kobrynska, V. M. Pushkarev, N. I. Levchuk, B. B. Guda, I. I. Komisarenko, O. V. Furmanova, O. I. Kovzun

SI «V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine», Kyiv, Ukraine

kobnatttaaa@gmail.com

Medullary thyroid carcinoma (MTC) arises from non-epithelial parafollicular cells. Lymph node metastases are common in MTC, with distant metastases being rare [1]. Papillary thyroid carcinoma (PTC) is the most frequent subtype, accounting for 85–90 % of all thyroid tumors. Despite its generally favourable prognosis, PTC is characterized by a relatively high frequency of regional lymphatic metastasis (Mts), which significantly affects recurrence risk and disease course [2, 3].

Monocyte chemoattractant protein-1 (MCP-1), also designated CCL2, is a member of the C-C chemokine superfamily that orchestrates the recruitment of monocytes and macrophages to sites of tissue injury and inflammation. The MCP subfamily comprises at least four ligands (MCP-1/CCL2, MCP-2/CCL8, MCP-3/CCL7, and MCP-4/CCL13), which share structural homology and partially receptors. MCP-1 signals predominantly through the G protein-coupled principal receptor CCR2, although it can also interact with ACKR1, CCR5, CCR10, and CCR11, with CCR2 [4-6]. The MCP-1 gene (*SCYA2*) is located on human chromosome 17q11.2-q21.1 with three exons and two introns [7]. The encoded precursor protein contains 99 amino acids, including a 23-amino-acid N-terminal signal peptide that is cleaved to generate the mature 76-amino-acid chemokine. The N-terminal residues, particularly positions 1-6, are critical for receptor engagement and chemotactic activity [4, 6, 7].

MCP-1 is known as tumor-derived chemotactic factor, as a wide variety of tumor cells can produce it. In addition, MCP-1 is secreted by a range of cell types in the tumor microenvironment (TME), such as cancer-associated

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fibroblasts, tumor-infiltrating monocytes, endothelial cells and tumor-associated adipocytes [8, 9].

Accumulating evidence implicates MCP-1 in the pathogenesis of autoimmune and metabolic disorders and, importantly, in multiple hallmarks of cancer. Elevated MCP-1 expression within the TME correlates with enhanced tumor invasion, metastatic dissemination, angiogenesis, and immunomodulation. Mechanistically, activation of the MCP-1/CCR2 axis triggers canonical oncogenic pathways — including PI3K/Akt/mTOR, ERK/GSK-3β/Snail, c-Raf/MEK/ERK, and broader MAPK cascades — thereby promoting cell survival, epithelial-mesenchymal transition, motility, and extracellular matrix remodeling. Preclinical studies indicate that pharmacologic or antibody-mediated blockade of MCP-1/CCR2 signaling can attenuate tumor growth and metastatic progression, underscoring its therapeutic relevance [5, 10].

Against this background, the present study **aimed** to comparatively evaluate MCP-1 levels in conditionally normal thyroid tissue, medullary thyroid carcinoma tissue, and metastatic lesions, as well as in blood plasma from patients with medullary thyroid carcinoma and papillary thyroid carcinoma with and without metastases, in order to clarify the tissue-systemic distribution pattern of MCP-1 in thyroid tumor progression.

MATERIALS AND METHODS

The research protocol was approved by the Bioethics Commission of SI Komisarenko Institute of Endocrinology and Metabolism, National Academy of Medical Sciences of Ukraine, protocol no. 26-KE dated April 10, 2019. All patients signed informed consent for the use of biomaterials for further diagnostic and scientific research.

Postoperative samples of 2 types of goiters, PTC, Mts, and CN (non-tumor, morphologically unchanged thyroid tissue) tissue, obtained from the surgical department of the Institute's clinic, were used for research. Blood plasma of the same MTC patients were analysed. Blood was obtained always before surgery by standard venipuncture and stored in EDTA tubes. Plasma was separated by centrifugation within 10 minutes after blood sampling. The concentration of protein in tissue lysates was determined according to Bradford method [11]. Blood controls were taken from healthy individuals without thyroid and comorbid diseases.

Samples were stored at −80 °C until use. The amount of MCP-1 was determined using enzyme immunoassay kits E-EL-H6005 (Elabscience, China). Measurements were performed at an optical wavelength of 450/630 nm on an immunoenzymatic plate analyzer Stat Fax 3200 (Awareness Technology, USA).

Patients with MTC, MTC + Mts, PTC, PTC + Mts participated in the study. Groups included 8 samples with MTC without Mts and 12 samples with metastatic MTC. The concentration of MCP-1 in plasma of 7 patients with PTC without Mts, 7 patients with metastatic PTC, 3 patients with MTC without Mts, and 5 patients with MTC without Mts was also determined.

Statistical analysis and data presentation were performed using Origin 2019b software. The results of the study are presented as M ± SE. Student's *t*-test and nonparametric tests was used to compare data groups. Values of $p \leq 0.05$ were considered significant.

RESULTS AND THEIR DISCUSSION

Monocyte chemoattractant protein-1 (MCP-1/CCL2) levels were significantly elevated in medullary thyroid carcinoma tissues compared with corresponding conditionally normal (CN) thyroid samples. In patients with non-metastatic medullary thyroid carcinoma (MTC), MCP-1 concentrations were nearly two-fold higher than in paired CN tissue (Table, groups 1–2; Fig. 1). In metastatic MTC, tumor MCP-1 levels exceeded those of adjacent CN tissue by more than three-fold (Table, groups 3–4; Fig. 1). The highest MCP-1 concentrations were detected in metastatic lymph node lesions (Group 5), indicating progressive upregulation along the primary tumor-metastasis axis.

Importantly, CN tissues adjacent to metastatic tumors exhibited significantly lower MCP-1 levels compared with CN tissues adja-

Table

The MCP-1 levels in blood and postoperative tissue samples from patients with medullary thyroid carcinoma and papillary thyroid carcinoma

No.	Tissue	MCP-1 pg/mkg	SE	n
1	CN	11.36	1.08	5
2	MTC	21.19	9.79*	5
3	CN	5.05	3.24+	5
4	MTC + Mts	15.32	6.99*	5
5	Mts	24.33	6.62*	5
No.	**Plasma**	**MCP-1 pg/mL**	**SE**	
1	Control	65.61	14.19	5
2	PTC	112.05	22.31	7
3	PTC + Mts	119.30	22.38	7
4	MTC	145.78	37.82	5
5	MTC + Mts	206.13	23.62^	5

Notes:
* — indicate significant differences from the conditionally normal tissue, $P \leq 0.05$;
+ — significant difference from the group 1 CN tissue, $P \leq 0.05$;
^ — significant difference from the group 3 MTC samples, $P \leq 0.05$

Abbreviations:
CN — conditionally normal tissue;
MTC — medullary thyroid carcinoma;
MTC + Mts — medullary thyroid carcinoma with metastasis (Mts);
PTC — papillary thyroid carcinoma without metastasis;
PTC + Mts — papillary thyroid carcinoma with metastasis.

cent to non-metastatic tumors (Groups 1 vs. 3), suggesting tumor-dependent remodelling of the peritumoral microenvironment. This observation supports the concept of reciprocal crosstalk

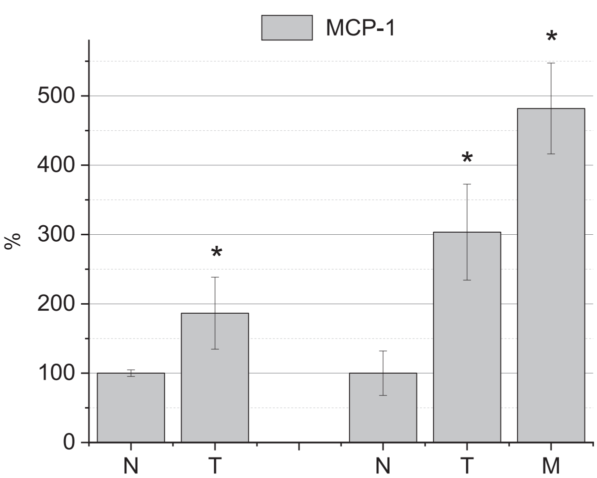

Fig. 1. Percentage of MCP-1 concentrations in the medullary thyroid carcinoma.

Notes: * – indicate significant differences from the conditionally normal tissue, $P \leq 0.05$.

Abbreviations: N – conditionally normal tissue; T – medullary thyroid carcinoma; M – metastasis.

between carcinoma cells and surrounding thyroid parenchyma [12, 13].

In plasma samples, MCP-1 concentrations did not differ significantly between patients with non-metastatic and metastatic papillary thyroid carcinoma (PTC) (Fig. 2). In contrast, circulating MCP-1 was markedly elevated in patients with metastatic MTC compared with non-metastatic MTC, indicating that systemic MCP-1 may reflect metastatic burden specifically in MTC rather than in PTC. These findings point to histotype-specific differences in chemokine regulation and systemic inflammatory responses.

MCP-1 is a pivotal regulator of tumor-associated inflammation, acting primarily through recruitment of CCR2-positive monocytes and macrophages to the tumor microenvironment. Accumulating evidence indicates that MCP-1 promotes metastasis by enhancing tumor-associated macrophage (TAM) infiltration, stimulating angiogenesis, and activating pro-survival and pro-migratory signalling pathways, including PI3K/Akt, ERK, MAPK, and STAT3 [10, 14, 15].

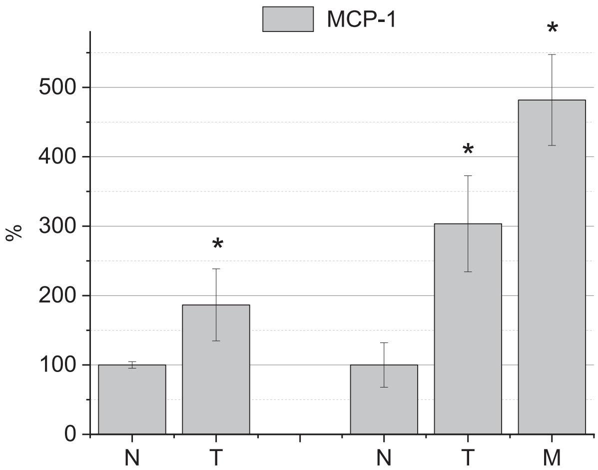

Fig. 2. Percentage of MCP-1 concentrations in the blood plasma of PTC and MTC patients with and without Mts.

Notes: * — significantly different from previous group, $P \leq 0.05$.

Abbreviations: see Table.

There is a study, which shows a significant relationship between the MCP-1 expression in tumor cells and the occurrence of lymph node metastases in patients with PTC. Furthermore, the expression levels of MCP-1 in tumor cells were significantly higher in patients with recurrent PTC than in those without recurrence. This study was the first to describe an association between the expression of MCP-1 in PTCs and aggressive behavior of this cancer. Mechanistically, MCP-1 enhances migration and invasion of thyroid cancer cells, partly via PI3K-dependent pathways [16].

It was also demonstrated that conditioned medium (CM) from the thyroid cancer SW579 cell line significantly elevated the expression of pro-inflammatory cytokines MCP-1, IL-1β, and HMGB-1 in human pulmonary microvascular endothelial cells [17].

It has been shown that TAMs contribute to the aggressiveness of anaplastic thyroid cancer (ATC). Cytokine assays revealed five commonly enriched cytokines (MCP-1, IL-6, IL-8, TIMP-1, and TGF-β1) in the CM derived from each of the three ATC cell lines. These cytokines, together, mimicked full CM activity in the induction of M2 macrophages. Further, they collaboratively activated STAT3, ERK, and PI3K-AKT signalling to facilitate the induction of M2. Importantly, CM-induced M2 could secrete soluble growth factors to promote ATC cell proliferation [18].

Other data show that thyroid hormones in the presence of either MCP-1 or IGF-1 are able to inhibit cell migration in THP-1 monocytes; the effect is mediated by integrin αvβ3. MCP-1 mediate their effects through a G-protein receptor, with an increase of cAMP, PI3K activation, and a tyrosine phosphorylation leading to the activation of STAT-1α, and actin polymerization. This implies also the activation of the MAPK pathway [19].

Beyond thyroid malignancies, MCP-1 overexpression has been linked to tumor progression in multiple solid cancers. In breast carcinoma, particularly triple-negative subtypes, MCP-1 promotes macrophage recruitment, angiogenesis, and metastatic dissemination. In prostate cancer, activation of the MCP-1/CCR2 axis drives tumor growth, bone colonization, and NF-κB-mediated invasion. Similar pro-metastatic roles have been documented in ovarian, esophageal, head and neck, and osteosarcoma models, where MCP-1 activates MAPK, AP-1, ERK, Akt, and STAT3 signalling networks [7, 20–23].

Interestingly, pancreatic cancer represents a potential exception: elevated circulating MCP-1 has been associated with increased apoptosis and improved survival in certain cohorts, suggesting context-dependent effects. This duality underscores the complexity of MCP-1 biology, which may vary according to tumor type, microenvironmental composition, and stage of disease [7, 23].

Thus, MCP-1 may be useful as marker of metastatic process in thyroid cancer, together with previously established factors: HIF-1α [24], MMP-2, [25], main EMT driver TGF-1β [26], tight junction zonula occludens-1 protein [27], and key EMT transcription factor ZEB1 [28].

CONCLUSION

The present data demonstrate a stepwise increase in MCP-1 levels from non-metastatic to metastatic medullary thyroid carcinoma and further to lymph node metastases, consistent with its role in metastatic progression. The selective elevation of plasma MCP-1 in metastatic medullary thyroid carcinoma — but not in papillary thyroid carcinoma — suggests that systemic chemokine dynamics differ between thyroid cancer histotypes, which may be associated with the tissue origin of the tumors. Given the established role of MCP-1 in macrophage recruitment and angiogenic remodelling, its upregulation in metastatic lesions likely reflects intensified tumor — stroma interactions that facilitate dissemination.

Collectively, these findings support MCP-1 as a mediator of tumor aggressiveness in medullary thyroid carcinoma and reinforce its potential utility as a biomarker of metastatic progression and as a candidate therapeutic target within the tumor microenvironment.

LIMITATIONS

This study has several limitations. It was conducted at a single center; therefore, the findings require validation in large-scale, multicenter studies. In addition, the relatively small number of patients in the overall cohort and in individual subgroups may have influenced the measured levels of the studied parameters.

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LEVEL OF MONOCYTE CHEMOATTRACTANT PROTEIN-1 IN MEDULLARY AND PAPILLARY THYROID CARCINOMAS

N. Ya. Kobrynska, V. M. Pushkarev, N. I. Levchuk, B. B. Guda, I. I. Komisarenko, O. V. Furmanova, O. I. Kovzun

SI «V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine», Kyiv, Ukraine
kobnatttaaa@gmail.com

Monocyte chemoattractant protein-1 (MCP-1), also known as C-C motif chemokine ligand 2 (CCL2), is a prototypical member of the C-C chemokine superfamily (MCP-1/2/3/4) that signals through G protein–coupled receptors to orchestrate leukocyte recruitment. By regulating the trafficking and activation of monocytes and basophils, MCP-1 critically modulates inflammatory responses. In the oncologic context, MCP-1 promotes tumor progression and metastatic dissemination through the recruitment of tumor-associated macrophages, thereby fostering a microenvironment conducive to cancer cell survival, migration, and invasion. This study **aimed** to comparatively evaluate MCP-1 levels in conditionally normal (CN) thyroid tissue, primary medullary thyroid carcinoma (MTC) tissues, and corresponding metastatic (Mts) lesions, as well as in blood plasma from patients with medullary thyroid carcinoma and papillary thyroid carcinoma (PTC) with and without metastases.

Materials and methods. Postoperative thyroid tissue specimens and peripheral blood plasma were collected from patients undergoing surgical treatment. MCP-1 concentrations were quantified using enzyme-linked immunosorbent assay (ELISA).

Results. MCP-1 expression was significantly elevated in primary MTC tissues without metastases compared with matched CN thyroid tissue. In metastatic MTC, tissue MCP-1 levels were increased more than threefold relative to corresponding normal tissue, with the highest expression observed in lymph node metastatic deposits. Consistently, circulating MCP-1 concentrations were significantly higher in patients with metastatic MTC than in those with non-metastatic disease. No significant difference in plasma MCP-1 concentration was found between metastatic PTC and PTC without metastases.

Conclusions. MCP-1 expression is markedly upregulated in metastatic versus non-metastatic medullary thyroid carcinoma at both tissue and systemic levels. These findings implicate MCP-1 as a potential preoperative biomarker for stratifying metastatic risk in medullary thyroid carcinoma.

Keywords: monocyte chemoattractant protein-1, medullary thyroid carcinoma, papillary thyroid carcinoma, metastasis, biomarker.

РІВЕНЬ ХЕМОАТРАКТАНТНОГО БІЛКА-1 МОНОЦИТІВ ПРИ МЕДУЛЯРНІЙ ТА ПАПІЛЯРНІЙ КАРЦИНОМАХ ЩИТОПОДІБНОЇ ЗАЛОЗИ

Кобринська Н. Я., Пушкарьов В. М., Левчук Н. І., Гуда Б. Б., Комісаренко І. І., Фурманова О. В., Ковзун О. І.

ДУ «Інститут ендокринології та обміну речовин ім. В. П. Комісаренка НАМН України»; м. Київ, Україна

kobnatttaaa@gmail.com

Хемоатрактантний білок-1 моноцитів (MCP-1), також відомий як ліганд хемокінів C-C мотиву 2 (CCL2), є прототиповим членом надродини хемокінів C-C (MCP-1/2/3/4), сигналінг якого здійснюється через рецептори, пов'язані з G-білком, організуючи рекрутинг лейкоцитів. Завдяки регуляції транспорту та активації моноцитів і базофілів MCP-1 критично модулює запальні реакції. В онкологічному контексті MCP-1 сприяє прогресуванню пухлини та метастатичному поширенню шляхом рекрутингу пухлинно-асоційованих макрофагів, створюючи мікросередовище, сприятливе для виживання, міграції та інвазії ракових клітин. Дослідження мало на **меті** порівняти рівні MCP-1 в умовно нормальній (УН) тканині щитоподібної залози (ЩЗ), тканині первинної пухлини медулярної карциноми щитоподібної залози (МКЩЗ) та її метастазах (Мтс), а також у плазмі крові пацієнтів з медулярною карциномою щитоподібної залози та папілярною карциномою щитоподібної залози (ПКЩЗ), як із метастазами, так і без них.

Матеріали та методи. Післяопераційні зразки тканини ЩЗ та плазми периферичної крові були отримані від пацієнтів, які пройшли хірургічне лікування. Концентрація MCP-1 визначалася за допомогою імуноферментного аналізу (ІФА).

Результати. Експресія MCP-1 була значно підвищена у тканині первинної пухлини МКЩЗ без метастазів порівняно з відповідною УН тканиною ЩЗ. У тканині метастатичної МКЩЗ рівні MCP-1 були підвищені більш ніж утричі порівняно з відповідною нормальною тканиною, причому найвища експресія спостерігалася в метастатичних ураженнях лімфатичних вузлів. Відповідно, концентрації MCP-1 у крові були вищими у пацієнтів із метастатичним МКЩЗ порівняно з пацієнтами з неметастатичною формою захворювання. Не було виявлено суттєвої різниці в концентрації MCP-1 у плазмі між метастатичним ПКЩЗ та ПКЩЗ без метастазів.

Висновки. Експресія MCP-1 значно підвищена при метастатичній медулярній карциномі щитоподібної залози порівняно з неметастатичною формою як на тканинному, так і на системному рівнях. Ці дані вказують на те, що MCP-1 може слугувати потенційним передопераційним біомаркером для стратифікації ризику метастазування при медулярній карциномі щитоподібної залози.

Ключові слова: моноцитарний хемоатрактантний білок-1, медулярна карцинома щитоподібної залози, папілярна карцинома щитоподібної залози, метастазування, біомаркер.