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Altered proinflammatory cytokine response in colorectal cancer patients: insights into immune dysregulation

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Abstract. *Introduction.* Colorectal cancer (CRC) is one of the most common oncological diseases, the pathogenesis of which is closely associated with the development of inflammation. The study of inflammation regulation, including the balance of pro- and antiinflammatory cytokines, is a promising topic for research, allowing for a deeper understanding of the pathogenesis of CRC and improving clinical approaches to the treatment for and diagnosis of this disease. This study investigates the altered secretion of proinflammatory cytokines, i.e., TNF-α and IL-1β, in CRC patients, aiming to elucidate immune dysregulation mechanisms. We sought to investigate the secretion characteristics of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), in patients with CRC.

Materials and methods. We enrolled 25 newly diagnosed CRC patients and 20 age- and sex-matched controls. Monocytes were isolated from the peripheral blood of participants using magnetic separation based on the CD14 marker. The isolated monocytes were cultured and subjected to dual stimulation with bacterial lipopolysaccharide at 24 hours and 7 days, followed by quantitative measurement of basal and stimulated cytokine levels using an enzyme-linked immunosorbent assay (ELISA).

Results. We revealed a significant reduction in TNF-α secretion in CRC monocytes after initial LPS stimulation, with no subsequent recovery upon restimulation. In contrast, IL-1β secretion elevated markedly in CRC patients, particularly after restimulation. These results suggest an impaired TNF-α response and an exacerbated IL-1β response in CRC, indicating a potential immune tolerance mechanism that may contribute to tumor progression. The distinct cytokine dynamics observed point at complex immune dysregulation within the CRC microenvironment.

Conclusion. The observed cytokine secretion patterns may indicate immune dysregulation in the microenvironment of CRC. Our study underscores the importance of understanding the specific roles of cytokines in CRC pathogenesis and highlights the potential for targeted therapeutic interventions to modulate these immune responses. Further research is necessary to explore the underlying signaling pathways and the broader implications of these findings for CRC treatment strategies. This work provides critical insights into the pro-inflammatory cytokine profiles in CRC, advancing our understanding of the immune landscape in cancer and opening new avenues for therapeutic exploration.

Keywords: colorectal cancer, cytokines, tumor necrosis factor-alpha, interleukin-1 beta, immune tolerance

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Измененный провоспалительный цитокиновый ответ у пациентов с колоректальным раком как признак иммунной дисрегуляции

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Резюме. *Введение.* Колоректальный рак является одним из самых распространенных онкологических заболеваний, чей патогенез тесно связан с развитием воспаления. Изучение регуляции воспаления, в том числе баланса провоспалительных и противовоспалительных цитокинов, – перспективная тема для исследования, позволяющая глубже понять патогенез колоректального рака и улучшить клинические подходы в лечении и диагностике этого заболевания. В данной работе изучена секреция провоспалительных цитокинов, таких как фактор некроза опухолей альфа (TNF-α) и интерлейкин-1 бета (IL-1β), у пациентов с колоректальным раком с целью выяснения механизма иммунной дисрегуляции.
Материалы и методы. Проведено исследование особенностей секреции провоспалительных цитокинов – TNF-α и IL-1β у пациентов с колоректальным раком. В исследование были включены 25 пациентов с колоректальным раком и 20 сопоставимых по возрасту и полу участников из группы сравнения. Из периферической крови участников методом магнитной сепарации по маркеру CD14 были выделены моноциты. Моноциты культивировали и подвергли двойному стимулированию бактериальным липополисахаридом через 24 часа и через 7 суток с количественным определением базальных и стимулированных уровней цитокинов иммуноферментным методом.
Результаты. Результаты исследования показали значительное снижение секреции TNF-α в культуре моноцитов после первоначального стимулирования липополисахаридом без последующего восстановления уровня секреции при повторной стимуляции. Секреция IL-1β, напротив, была значительно повышена у пациентов с колоректальным раком, особенно после повторной стимуляции. Эти результаты свидетельствуют об измененном цитокиновом ответе, выражающемся в истощении секреции TNF-α и усиленной секреции IL-1β у пациентов с колоректальным раком, что может способствовать развитию иммунной толерантности опухоли.
Заключение. Наблюдаемая особенность секреции цитокинов может указывать на иммунную дисрегуляцию в микроокружении колоректального рака. Наше исследование подчеркивает значимость изучения роли цитокинов в патогенезе колоректального рака и может быть основой для изучения терапевтической коррекции изменений цитокинового ответа у пациентов с колоректальным раком.

Ключевые слова: колоректальный рак, цитокины, фактор некроза опухоли-альфа, интерлейкин-1 бета, иммунная толерантность

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Introduction

Colorectal cancer (CRC) represents a significant global health burden ranking as the third most common cancer worldwide. The pathogenesis of CRC is complex and involves a multifaceted interplay between genetic, environmental, and immunological factors. Central to this process is the tumor microenvironment (TME) which includes various cellular and molecular components that collectively

influence cancer progression. Among these components, inflammation plays a crucial role in both the initiation and progression of CRC.

Inflammation is increasingly recognized as a key factor in the development of many cancers, including CRC. Chronic inflammation in the colon, as seen in conditions such as inflammatory bowel disease, significantly elevates the risk of developing CRC [1]. This is largely due to the persistent presence of pro-inflammatory cytokines, reactive oxygen species, and other mediators that can induce genetic mutations and promote a favorable environment for tumorigenesis.

Macrophages, a critical component of the immune system, are highly plastic cells capable of adopting various functional phenotypes in response to environmental signals. In the context of CRC, macrophages can exhibit either a pro-inflammatory (M1) or anti-inflammatory (M2) phenotype. M1 macrophages are characterized by their ability to produce high levels of pro-inflammatory cytokines, such as TNF-α and IL-1β, which can promote anti-tumor immunity. Conversely, M2 macrophages are associated with tissue repair and immunosuppression, often contributing to tumor growth and metastasis by secreting anti-inflammatory cytokines and growth factors [2, 3].

The role of macrophage reactivity and cytokine secretion in CRC is of particular interest. Pro-inflammatory cytokines, including TNF-α and IL-1β, play pivotal roles in modulating the immune response and influencing the behavior of other cells within the TME. TNF-α is involved in promoting inflammation and apoptosis, while IL-1β is known to enhance the inflammatory response and has been implicated in contributing to angiogenesis and tumor invasiveness [4, 5].

In CRC, the balance between these cytokines can significantly impact disease progression. Dysregulated cytokine production can lead to chronic inflammation that supports tumor growth and immune evasion. For instance, elevated levels of IL-1β have been associated with increased tumor aggressiveness and poorer prognosis in CRC patients [6]. Similarly, aberrant TNF-α signaling has been linked to both tumor-promoting and tumor-suppressing effects, depending on the context and timing of its expression [7, 8].

Understanding the dynamics of cytokine secretion and macrophage reactivity in CRC is crucial for developing targeted therapies aimed at modulating the immune response. By elucidating the mechanisms underlying the altered cytokine profiles in CRC patients, we can identify potential biomarkers for disease progression and therapeutic targets to improve patient outcomes. This study aimed to provide insights into specific alterations in TNF-α and IL-1β secretion by monocytes in CRC patients, shedding light on the complex interplay between inflammation and cancer.

Materials and methods

Study participants

The study encompassed 45 participants: 25 newly diagnosed colorectal adenocarcinoma patients and 20 age- and sex-matched controls. We excluded subjects with specific acute and chronic diseases. Only individuals who had not yet undergone any therapeutic interventions, such as chemotherapy, or radiation therapy, were included. All procedures, including comprehensive post-operative pathomorphological analysis, adhered to the 1975 Helsinki Declaration and its 2013 update. All stages of the study comply with the legislation of the Russian Federation and regulatory documents of the research organization. Written informed consents were obtained from all participants. The research protocol No. 8 was approved by the local ethical committee of the Petrovsky National Research Center of Surgery on October 20, 2022.

Monocyte culture isolation and double lipopolysaccharide stimulation assay

Mononuclear cells were isolated from 30-ml blood samples via Ficoll density gradient centrifugation, followed by CD14+ cell immunomagnetic separation using LS Columns and CD14+ MicroBeads (Miltenyi Biotec Inc., USA). Isolated CD14+ monocytes were cultured at 1,000,000 cells/ml in X-VIVO serum-free medium (Lonza, Switzerland) with L-glutamine, gentamicin, and phenol red, at 37°C and 5% CO_2. Triplicate cultures were established per patient. Lipopolysaccharides (LPSs) from *Escherichia coli* 0111:B4 (Sigma-Aldrich, USA) were used for stimulation at a concentration of 1 μg/ml. Two healthy patients received LPS on day 1, with the third serving as a control. Cytokine levels were assessed at 24-hour intervals and after a medium refresh. Restimulation with LPS occurred in one healthy individual on day 6. The medium was collected on day 7 for final cytokine analysis and stored at –70°C until assayed for TNF-α and IL-1β concentrations.

Measurement of TNF-α and IL-1β concentrations

TNF-α and IL-1β concentrations in the culture medium were quantified using ELISA kits (Human TNF-alpha/TNFSF1A DuoSet ELISA and Human IL-1beta/IL-1F2 DuoSet ELISA; R&D Systems Inc., USA). Assessments included the following figures: 1) basal cytokine levels after 24 hours without LPS (nonstimulated), 2) cytokine levels after 24 hours of LPS stimulation (first stimulation), 3) basal cytokine levels on day 7 in cultures not restimulated with LPS (non-restimulated), and 4) cytokine levels on day 7 following a 24-hour LPS restimulation (restimulation).

Statistical analysis

We performed statistical analysis using SPSS Statistics v. 26.0. Data distribution and differences between the CRC and control groups were assessed with the Shapiro-Wilk test and Mann-Whitney U-test, respectively. Quantitative results are presented as median and interquartile range.

Results

Table 1 provides characteristics of study participants.

In our study, we aimed to investigate the differential cytokine responses of blood monocytes in CRC patients

Table 1 | Таблица 1

Characteristics of study participants | Характеристика участников исследования

Characteristics | Характеристика	Control Group (n=20) | Группа сравнения	CRC Patients (n=25) | Пациенты с КРР
Age (years) | Возраст (лет)	58 (56–63)	61 (59–65)
Sex, M/F | Пол, м/ж	13/7	14/11
CRC Stage: | Стадия КРР		
T3N0M0	–	12
T3N1aM0	–	6
T1N0M0	–	2
T3N2bM1a	–	1
T3N1cM0	–	1
T4bN2aM0	–	1
T4bN2bM1c	–	1
T4bN2bM0	–	1

CRC – colorectal cancer | КРР – колоректальный рак

and healthy controls to LPS stimulation. We focused on TNF-α and IL-1β, given their pivotal roles in modulating tumor inflammation and their distinct cellular mechanisms [9, 10].

Upon LPS stimulation, we found that monocytes from CRC patients exhibited an initial secretion of TNF-α, followed by an exhaustion in its secretion. Specifically, a lower basal level was observed after a 7-day culture and minimal increase upon LPS restimulation (Table 2). Conversely, IL-1β secretion showed elevated baseline levels and increased responsiveness to restimulation in CRC patients (Table 2).

Discussion

Our study elucidates differential cytokine secretion patterns in blood monocytes from CRC patients as compared to that in healthy controls. Specifically, monocytes in CRC show an exhaustion in TNF-α secretion and an elevated IL-1β secretion following LPS stimulation. These cytokines serve distinct roles in inflammatory processes, regulated via unique pathways and kinetic profiles [11–13]. We revealed a marked reduction in TNF-α secretion by monocytes in CRC patients after initial LPS stimulation, with no significant recovery upon restimulation. This suggests a potential exhaustion or dysfunction of monocytes, which could impair the body's ability to mount an effective inflammatory

Table 2 | Таблица 2

Levels of TNF-α and IL-1β Secretion | Уровень секреции TNF-α и IL-1β

		Control Group | Группа сравнения	CRC patients | Пациенты с КРР	p (U-test) | p (U-тест)
TNF-α concentration (pg/ml) | Концентрация TNF-α (пг/мл)				
Level at 24 hours | Уровень через 24 часа	Nonstimulated | Нестимулированный	135 (89–199)	97 (79–134)	1.0
	First LPS stimulation | Первая стимуляция ЛПС	3,356 (2,740–5,030)	4,503 (2,532– 7,148)	0.222
Level at 7 days | Уровень через 7 дней	Non-restimulated | Нерестимулированный	148 (99–169)	4 (2–5)	0.001*
	Restimulation with LPS | Рестимуляция ЛПС	141 (92–185)	7 (4–9)	0.001*
IL-1β concentration (pg/ml) | Концентрация IL-1β (пг/мл)				
Level at 24 hours | Уровень через 24 часа	Nonstimulated | Нестимулированный	114 (66–208)	274 (264–328)	0.001*
	First LPS stimulation | Первая стимуляция ЛПС	984 (856–1,101)	1,258 (1,198–1,581)	0.008*
Level at 7 days | Уровень через 7 дней	Non-restimulated | Нерестимулированный	120 (106–147)	187 (175–203)	0.001*
	Restimulation with LPS | Рестимуляция ЛПС	123 (82–148)	248 (215–288)	0.001*

LPS – lipopolysaccharide; CRC – colorectal cancer | ЛПС – липополисахарид; КРР – колоректальный рак.
* Statistically significant difference between the control group and CRC patients | * Статистически значимые различия между группой сравнения и пациентами с КРР

response against tumor cells. The inability to sustain TNF-α production could facilitate immune evasion by the tumor, contributing to its progression and metastasis. Conversely, IL-1β secretion was significantly elevated in colorectal cancer patients, especially following restimulation. IL-1β is known to enhance inflammatory responses and has been implicated in promoting tumor invasiveness and angiogenesis. The heightened IL-1β levels may reflect a state of chronic inflammation within the colorectal cancer microenvironment, which could support tumor growth and spread.

The exhaustion of TNF-α secretion could indicate an impaired proinflammatory response, facilitating immune evasion by tumor cells. TNF-α plays a dual role in cancer, potentially promoting antitumor immunity through its inflammatory effects, while also being capable of promoting tumor growth under certain conditions [7, 8]. The inability of monocytes to sustain TNF-α production in CRC patients may impair effective immune surveillance and response, contributing to tumor progression.

The TNF-α pathway, primarily modulated through NF-κB signaling, is involved in acute inflammation and cellular survival mechanisms, including apoptosis via Fas receptors [11].

IL-1β is a potent proinflammatory cytokine that activates immune cells and is regulated through the NLRP3 inflammasome pathway [10]. In our findings, IL-1β secretion was significantly elevated in CRC patients, particularly after restimulation with LPS. This heightened IL-1β level suggests a state of chronic inflammation within the CRC microenvironment, which is conducive to tumor growth and metastasis. IL-1β has been implicated in promoting angiogenesis, tumor invasiveness, and creating a protumorigenic inflammatory milieu [14]. The elevated IL-1β in CRC patients could thus reflect an environment that supports cancer cell survival and dissemination.

IL-1β, conversely, activates immune cells and is regulated through the NLRP3 inflammasome pathway [12, 13]. The secretion kinetics of these cytokines are divergent as well, with TNF-α peaking within 1–2 hours after LPS exposure and IL-1β reaching a peak at 4–6 hours [11–13].

These findings raise questions about altered immune responses in CRC. Monocytes in CRC patients may undergo a form of "tolerization," reducing their efficacy against tumors and potentially fueling the tumor microenvironment. The abnormal cytokine secretion patterns observed underscore the complexity of CRC pathogenesis and the role of chronic inflammation therein.

The altered secretion profiles in CRC potentially align with the theory that CRC is an inflammation-associated malignancy. This leads us to several hypotheses that warrant further investigation:

1. Acquired immune tolerance in monocytes could serve as a protective mechanism for tumor cells against immune attack [15, 16]. This could particularly be relevant given that IL-1β secretion is elevated in CRC patients, necessitating a broader cytokine panel for a complete understanding.
2. Abnormalities in key signaling pathways such as NF-κB and MAPK in monocytes could be pivotal in understanding the observed phenotypes [17].
3. The tumor microenvironment, a dynamic entity involving various soluble factors and exosomes, could influence the reduced TNF-α resecretion [18].
4. A depletion in monocyte count in CRC patients could also contribute to the observed exhaustion of TNF-α secretion [19].
5. CRC-associated alterations in gut microbiota and intestinal permeability could be influencing monocyte interactions and subsequent cytokine secretion [20].

Collectively, these results and hypotheses open up new avenues for future research aimed at elucidating the complex interplay between inflammation, immune responses, and CRC pathogenesis. To fully understand the altered cytokine dynamics, further research should explore the signaling pathways involved in TNF-α and IL-1β regulation. Investigating the roles of NF-κB, MAPK, and NLRP3 inflammasome pathways could provide deeper insights into the molecular mechanisms driving these changes. Expanding the cytokine panel to include other pro- and antiinflammatory mediators will help delineate the complex network of immune interactions in CRC. This could identify additional biomarkers for disease progression and potential therapeutic targets.

Longitudinal studies assessing cytokine levels throughout the course of CRC treatment could elucidate their prognostic value and guide the development of personalized immunotherapy strategies. Monitoring cytokine profiles may also help predict patient responses to existing therapies and improve treatment outcomes.

Understanding how the tumor microenvironment influences monocyte function and cytokine secretion will be crucial. Factors such as hypoxia, tumor-derived exosomes, and stromal cell interactions likely play significant roles in shaping the immune response in CRC.

Conclusion

The altered cytokine response observed in colorectal cancer patients highlights a significant dysregulation in immune function that may contribute to tumor progression. Our findings underscore the importance of cytokines, particularly TNF-α and IL-1β, in modulating the immune landscape within the colorectal cancer microenvironment.

The observed cytokine profile suggests that monocytes in colorectal cancer patients may undergo a form of "tolerization," reducing their efficacy in attacking tumor cells and potentially fostering a more permissive environment for tumor development. This immune tolerance could be a strategic adaptation by the tumor to evade immune surveillance.

These results indicate that targeting cytokine responses could be a viable strategy for colorectal cancer treatment. Modulating the immune response to restore effec-

tive TNF-α production while controlling excessive IL-1β secretion might improve antitumor immunity and inhibit tumor progression. Future therapies could focus on reversing monocyte exhaustion and reactivating their proinflammatory functions.

In conclusion, this study provides critical insights into the proinflammatory cytokine profiles in colorectal cancer, advancing our understanding of the immune dysregulation associated with cancer progression. These findings expand possibilities for therapeutic exploration aimed at modulating immune responses to improve patient outcomes in colorectal cancer.

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