European Journal of Clinical Pharmacy
Print ISSN: 2385-409X, **Online ISSN**: 3105-0409
Website: https://farmclin.com/

Dysregulated Inflammatory Cytokine Responses in Individuals with Colorectal Cancer: An Exploration of Immune Imbalance.

Article History:

Name of Author:
Nikolay Shakhpazyan[1],Nikolay Sadykhov[2],LiudmilaMikhaleva[3],Arkady Bedzhanyan[4],AlexandraKonyukova[5], KseniaMaslyonkina[6],Andrey Kontorschikov[7],Alexander Orekhov[8]

Affiliation: *[1]Avtsyn Research Institute of Human Morphology, Petrovsky National Research Center of Surgery, 119435, Moscow, Russia; nshakhpazyan@gmail.com*
[2]Research Institute of Human Morphology, Petrovsky National Research Center of Surgery, 119435, Moscow, Russia; drawnman@mail.ru
[3]Avtsyn Research Institute of Human Morphology, Petrovsky National Research Center of Surgery, 119435, Moscow, Russia; mikhalevalm@yandex.ru
[4]Department of Abdominal Surgery and Oncology II (Coloproctology and Uro-Gynecology), Petrovsky National Research Center of Surgery, 119435, Moscow, Russia; arkady.bedzhanyan@gmail.com
[5]Avtsyn Research Institute of Human Morphology, Petrovsky National Research Center of Surgery, 119435, Moscow, Russia; have.to.study@yandex.ru
[6]Avtsyn Research Institute of Human Morphology, Petrovsky National Research Center of Surgery, 119435, Moscow, Russia; Ksusha-voi@yandex.ru
[7]Avtsyn Research Institute of Human Morphology, Petrovsky National Research Center of Surgery, 119435, Moscow, Russia; andreistr.ru@mail.ru
[8]Laboratory of Angiopathology, Institute of General Pathology and Pathophysiology, Moscow 125315, Russia; Institute for Atherosclerosis Research, Moscow 121096, Russia; alexandernikolaevichorekhov@gmail.com

Corresponding Author:

Abstract: Background: This study examines pro-inflammatory cytokines tumor necrosis factor alpha (TNF-α) and interleukin 1beta (IL-1β) in colorectal cancer (CRC). Twelve CRC patients and 9 control individuals came in [Name of the clinic] from April to June 2023 were enrolled. Study participants were recruited using the Convenience Sampling method. The CRC (colorectal cancer) patient group consisted of individuals with morphologically confirmed colorectal cancer who were scheduled for radical surgical treatment, prior to the administration of any pharmacological or radiation therapy. Control group individuals were volunteers of comparable age and sex, without oncological or chronic diseases affecting the immune system or related to inflammation. Monocytes were isolated and analyzed through Double lipopolysaccharide (LPS) Stimulation Assay and enzyme-linked immunosorbent assay (ELISA). Results indicate diminished TNF-α secretion post-initial LPS stimulation and no recovery upon re-stimulation in CRC monocytes (132 pg/ml in the control group versus 4 pg/ml in the CRC group, p=0.007). Conversely, elevated IL-1β levels were observed, particularly after re-stimulation (115 pg/ml in the control group versus 249 pg/ml in the CRC group, p=0.01). The findings suggest altered cytokine dynamics in CRC and potential avenues for targeted therapeutic interventions.

Keywords: Colorectal cancer Inflammatory cytokines Immune imbalance Dysregulated immune response

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How to Cite: Shakhpazyan, N., Sadykhov, N., Mikhaleva, L., Bedzhanyan, A., Konyukova, A., Maslyonkina, K., Kontorschikov, A., & Orekhov, A. (n.d.). Dysregulated inflammatory cytokine responses in individuals with colorectal cancer: An exploration of immune imbalance. *European Journal of Clinical Pharmacy*. 2026. 8(1) 3261-3268

***Received**:* 20-03-2026
***Revised**:* 16-04-2026
***Accepted**:* 26-04-2026
***Published**:* 19-05-2026

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INTRODUCTION

Colorectal cancer (CRC) stands as a significant worldwide health concern, occupying the position of the third most prevalent form of cancer. Central to deciphering the mechanisms underlying CRC is the complex interplay among the tumor milieu, immune response, and inflammatory processes [1]. Cytokines such as Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-1beta (IL-1β) are central to this dynamic, each having distinct roles yet sometimes overlapping effects. TNF-α and IL-1β exhibit several significant differences in their mechanisms of secretion and activity. Both cytokines are regulated at the transcriptional level by NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells), a transcription factor that plays a key role in inflammatory responses [2]. TNF-α is synthesized as a transmembrane protein and is cleaved into its soluble form by the enzyme TNF-α converting enzyme (TACE) [3]. The production of TNF-α is rapidly induced in monocytes by various stimuli such as lipopolysaccharide (LPS), viruses, and other cytokines. TNF-α mRNA is constitutively present in monocytes, allowing for a swift response upon stimulation [4]. Unlike TNF-α, IL-1β is not stored pre-formed in cells. Its production involves two steps: transcription of the IL-1β gene into mRNA and then translation into a precursor protein, pro-IL-1β. The processing of pro-IL-1β into its active form requires the activation of the inflammasome, a multi-protein complex that activates caspase-1 [5]. This activation is typically a response to a range of stimuli including microbial products, ATP, or crystalline substances. The cytokines also differ in their mechanisms of release from the cell. The soluble form of TNF-α is released into the extracellular space after cleavage [6]. The release of IL-1β is not as straightforward as that of TNF-α. Since IL-1β lacks a signal peptide for classical secretion, it is released through mechanisms such as exocytosis of secretory lysosomes, shedding of microvesicles, or pyroptosis (a form of cell death associated with inflammation) [7, 8]. Both cytokines play critical roles in inflammation and immune response. However, their functions, while overlapping in some aspects, are distinct in their pathways and effects. TNF-α is recognized for its multifaceted and significant role in the carcinogenesis of colorectal cancer. Research indicates that TNF-α can exhibit pro-tumorigenic properties. For instance, colorectal cancer cells under the influence of TNF-α in culture tend to acquire a pro-metastatic phenotype, demonstrating enhanced proliferation and survival. This involves various mechanisms, including the activation of tumor cells through the STAT3 signaling pathway, leading to increased proliferative activity and survival [9]. The pro-tumorigenic effects of extracellular vesicles containing TNF-α are attributed to their impact on cellular processes involving NF-kB, LAMB3, PI3K/AKT signaling pathways [10]. The regulation of microRNA miR-21 expression is identified as crucial [11]. A pro-tumorigenic effect, marked by increased cell migration and invasion, is observed through the activation of TROP-2 (tumor-associated calcium signal transducer protein-2) expression by this cytokine [12]. Conversely, the anti-tumorigenic effects of anti-TNF-α antibodies have been observed in an orthotopic mouse model of colorectal cancer. This includes both a direct anti-

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tumorigenic effect and an influence on the stromal microenvironment, including reduced angiogenesis [13]. TNF-α plays a significant role in the development of colitis-associated colorectal cancer [14]. It has been noted that the level of TNF-α positively correlates with the presence of colorectal cancer metastases in lymph nodes in patients with tumor recurrence [15]. Additionally, the level of TNF-α is associated with the biological properties of the tumor, and elevated levels in the blood are observed in low-differentiated colorectal cancer [16]. However, the role of TNF-α in carcinogenesis is complex, and a reduction in TNF-α levels can also have a pro-tumorigenic effect [17]. Specifically, a decrease in TNF-α production by tumor-recruited monocytes leads to tumor progression related to myeloid to endothelial differentiation [18]. The influence of TNF-α levels on tumor pathogenesis may be linked to features of the tumor microenvironment. One mechanism influencing the anti-tumorigenic immune response is the polarization of tumor-associated macrophages (TAMs). It is known that M1 polarization of TAMs promotes the development of innate and adaptive immune responses against tumors, whereas M2 polarization supports tumor growth [19-21]. M1 polarization is characterized by the secretion of pro-inflammatory cytokines, including TNF-α, by TAMs [22, 23]. A decrease in TNF-α secretion may indirectly indicate a tendency towards M2 polarization of TAMs. Considering the migration of monocytes from blood to the tumor site and their subsequent transformation into TAMs, it is of interest to study the characteristics of the inflammatory response of monocytes in cancer patients. IL-1β exhibits a complex and, at times, contradictory influence on tumor biology. A well-established pro-tumoral mechanism of this cytokine involves its impact on the tumor stroma, encompassing remodeling and angiogenesis [24, 25]. Recent studies have revealed contradictory effects of IL-1β on the polarization of TAMs. Notably, IL-1β, a pro-inflammatory cytokine, has been shown to shift the balance towards M2 polarization of macrophages through the activation of the STAT3 signaling pathway via chemokine (C-X-C motif) ligand 8 (CXCL8) [26]. Additionally, IL-1β is capable of inducing apoptosis in M1-polarized macrophages, thereby potentially favoring a shift towards M2 polarization, which may have a pro-tumoral effect [27]. On the other hand, it has been observed that inhibition of IL-1β secretion, triggered by low expression of SHP-2, is associated with M2 polarization of TAMs in colorectal tumors [28]. The complexity of the tumor microenvironment and the multifaceted roles of cytokines such as IL-1β underscore the necessity for further research to attain a comprehensive understanding of their functions and interactions within the context of cancer biology. This study aims to scrutinize the roles of TNF-α and IL-1β, particularly their secretion by blood monocytes, to elucidate their individual and collective contributions to CRC.

Materials and Methods

Participant Recruitment and Group Formation

This is an observational study were observed and recorded the differences in cytokine dynamics between the CRC group and the control group. Participants in this study who visited [Name of the Clinic] from April to June 2023 were enrolled. The study participants were recruited using the Convenience Sampling method. Convenience sampling is a non-probabilistic sampling method where participants are selected based on their availability and willingness to take part in the study, rather than being randomly chosen. Convenience sampling is chosen for this study as it efficiently targets a specific patient group, is resource-effective for short-communication research, and ethically aligns with recruiting willing participants with specific medical conditions. Common inclusion criteria for all participants included being older than 18 and having a conscious desire to participate in the study, as expressed in a signed informed consent. Common exclusion criteria for all participants were critical cardiovascular conditions: Stage III-IV tissue ischemia, acute cerebral circulatory disturbance, acute coronary syndrome, myocardial infarction, and chronic heart failure of class III and IV according to The New York Heart Association (NYHA); Critical clinical conditions not directly related to cardiovascular diseases, including the need for urgent surgeries, chronic renal failure of stages IV-V (creatinine clearance < 30 ml/min according to the Cockroft-Gault formula); Severe disability of the patient (4 or higher on the modified Rankin Scale); Systemic autoimmune diseases in the anamnesis, including: rheumatoid arthritis, systemic lupus erythematosus, autoimmune thyroiditis, autoimmune vasculitides, ulcerative colitis. There were formed two groups: CRC (colorectal cancer) patient group and Control group The CRC (colorectal cancer) patient group consisted of individuals with morphologically confirmed colorectal cancer who were scheduled for radical surgical treatment, prior to the administration of any pharmacological or radiation therapy. The stage of the disease was confirmed by examining the surgical material. The Control group comprised volunteers, without oncological or chronic diseases affecting the immune system or related to inflammation, and without significant weight loss (more than 10%) over the past year. We used demographic matching approach - the Control group participants were matched for age and gender with the patient group.

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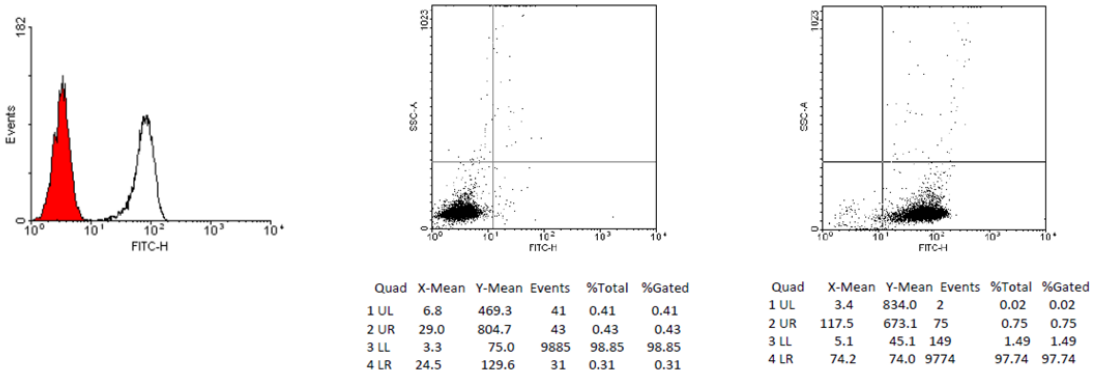
Study Participants

The investigation included a cohort of 21 subjects, comprising 12 individuals recently diagnosed with colorectal adenocarcinoma and an additional 9 controls who were matched for age and gender. Exclusion criteria filtered out individuals with specific acute and chronic diseases. Prior to any therapeutic intervention. All procedures, including comprehensive pathomorphological analysis post-surgery, adhered to the 1975 Helsinki Declaration and its 2013 update. Written informed consent was obtained from all participants.

Monocyte Culture Isolation and Double LPS Stimulation Assay

Mononuclear cells were extracted from blood samples of 30 ml utilizing Ficoll density gradient centrifugation, succeeded by the immunomagnetic separation of CD14+ cells employing LS Columns and CD14+ MicroBeads (Miltenyi Biotec Inc., USA). The purity of isolated monocytes confirmed by flow-cytometry (97.2±1.82% CD14+ cells) (Fig. 1). The isolated CD14+ monocytes were subsequently cultured in a concentration of one million cells per ml utilizing X-VIVO serum-free medium (Lonza, Switzerland), supplemented with gentamicin, L-glutamine, and phenol red, under conditions of 37°C and a 5% CO_2 atmosphere. Cultivation performed in cultural plates with 0.5 ml volume of cell-media suspension (500 000 cells) per a well. Triplicate cultures were established per patient. LPS stimulation was conducted at 1 µg/ml concentration of LPS. Two wells 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. Re-stimulation with LPS occurred in one well on day 6. Medium was collected on day 7 for final cytokine analysis and stored at -70°C until assayed for TNF-alpha and IL-1beta concentrations.



Quad	X-Mean	Y-Mean	Events	%Total	%Gated
1 UL	6.8	469.3	41	0.41	0.41
2 UR	29.0	804.7	43	0.43	0.43
3 LL	3.3	75.0	9885	98.85	98.85
4 LR	24.5	129.6	31	0.31	0.31

Quad	X-Mean	Y-Mean	Events	%Total	%Gated
1 UL	3.4	834.0	2	0.02	0.02
2 UR	117.5	673.1	75	0.75	0.75
3 LL	5.1	45.1	149	1.49	1.49
4 LR	74.2	74.0	9774	97.74	97.74

***Figure 1: Flow-cytometry analysis of a sample immunomagnetic separated* cells, 97.74% cells are CD14+.**

Measurement of TNF-alpha and IL-1beta Concentrations

Concentrations of TNF-alpha and IL-1beta in the culture medium were ascertained utilizing ELISA kits (Human TNF-alpha/TNFSF1A DuoSet ELISA and Human IL-1beta/IL-1F2 Duo-Set ELISA; R&D Systems Inc., USA). The evaluations were structured to encompass four distinct scenarios: 1) endogenous cytokine concentrations after a 24-hour period in the absence of LPS (termed non-stimulated), 2) cytokine concentrations at the 24-hour mark subsequent to initial LPS exposure (designated as first stimulation), 3) baseline cytokine concentrations on day 7 in cultures that had not received an additional LPS stimulation (termed non-re-stimulated), and 4) cytokine concentrations on the seventh day following a 24-hour period of LPS re-stimulation (designated as re-stimulation).

Statistical Analysis

Statistical evaluations were executed utilizing SPSS Statistics software, version 26.0. The distribution of data was appraised via the Shapiro-Wilk test to choose parametric or non-parametric statistical tests. Quantitative outcomes are delineated as median values accompanied by interquartile ranges. Disparities between the colorectal adenocarcinoma cohort and the control group were scrutinized employing the Mann-Whitney U-test. Additionally, bootstrap analysis [29] was conducted to estimate the variability and confidence intervals of our key statistics. This involved resampling our data with replacement to create numerous bootstrap samples, each equal in size to the original dataset. The resampling process was iterated 10,000 times, allowing for the robust estimation of the variability and confidence intervals for the median cytokine levels. A predetermined alpha level of 0.05 was set for all statistical tests to determine significance.

Results

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Participant group characteristics are presented in Table 1.

In our study, we aimed to investigate the differential cytokine responses of blood monocytes in CRC patients and healthy controls to LPS stimulation. We focused on TNF-alpha and IL-1beta, given their pivotal roles in modulating tumor inflammation and their distinct cellular mechanisms [30-32]. 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 re-stimulation (Table 2). Conversely, IL-1beta secretion showed elevated baseline levels and increased responsiveness to re-stimulation in CRC patients (Table 2). 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.

Table 2. Quantification of TNF-α and IL-1β Release

Analyte	Time point	Condition	Control	CRC	p-value (Mann-Whitney U test)
TNF-α concentration (pg/ml)	Concentration at 24 hours	Non-stimulated with LPS	111 (85-465)	108 (63-210)	0.743
	Concentration at 24 hours	Initial LPS Exposure	4498 (2456-7446)	3323 (2699-5708)	0.842
	Concentration at 7 days	LPS Non-Stimulation Condition	136 (79-179)	4 (2-5)	0.001*
	Concentration at 7 days	Re-stimulation with LPS	132 (79-182)	7 (4-10)	0.007*
IL-1β concentration (pg/ml)	Concentration at 24 hours	LPS Non-Stimulation Condition	96 (62-209)	273 (259-333)	0.005*
	Concentration at 24 hours	Initial LPS Exposure	1084 (422-4105)	1313 (1084-1626)	0.328
	Concentration at 7 days	LPS Non-Stimulation Condition	115 (87-162)	188 (176-212)	0.113
	Concentration at 7 days	Re-stimulation with LPS	115 (82-180)	249 (197-328)	0.01*

LPS, lipopolysaccharide; CRC, colorectal cancer. Statistical significance is indicated by an asterisk.

DISCUSSION

Our study elucidates differential cytokine secretion patterns in blood monocytes from CRC patients as compared to healthy controls. Specifically, monocytes in CRC show an exhaustion in TNF-α secretion and an elevated IL-1β secretion following LPS stimulation. As we mentioned, these cytokines serve distinct roles in inflammatory processes, regulated via unique pathways and kinetic profiles [19-23, 27, 28, 30-32]. Specifically, we noted exhaustion in TNF-α secretion and elevated IL-1β secretion following LPS stimulation. In CRC patients, the monocytes showed a reduced ability to secrete TNF-α after being stimulated with LPS. TNF-α is a cytokine involved in systemic inflammation and is one of the cytokines that make up the acute phase reaction. The term "exhaustion" here implies that these cells are less capable of producing TNF-α after stimulation, which could be significant in understanding the immune response in CRC. Conversely, these monocytes exhibited an increased production of IL-1β following LPS stimulation. IL-1β is another important cytokine in the body's inflammatory response, playing a role in cell proliferation, differentiation, and apoptosis (programmed cell death). These cytokines (TNF-α and IL-1β) have different roles in the body's inflammatory processes and are regulated through distinct pathways and kinetic profiles. This means that they are activated through different mechanisms in the body and have different timings in terms of their production and action [4, 5]. As an example, the TNF-α pathway, primarily modulated through NF-κB signaling, is involved in acute inflammation and cellular survival mechanisms, including apoptosis via Fas receptors [33]. IL-1β, conversely, activates immune cells and is regulated through the NLRP3 inflammasome pathway [34-35]. The secretion kinetics of these cytokines are divergent as well, with TNF-α peaking within 1-2 hours after LPS exposure, whereas IL-1β reaches a peak at 4-6 hours [33-35].

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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 [36]. 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 [37]. 3. The tumor microenvironment, a dynamic entity involving various soluble factors and exosomes, could influence the reduced TNF-α re-secretion [38]. 4. A depletion in monocyte count in CRC patients could also contribute to the observed exhaustion of TNF-α secretion [39]. 5. Lastly, CRC-associated alterations in gut microbiota and intestinal permeability could be influencing monocyte interactions and subsequent cytokine secretion [39].
Collectively, these findings and hypotheses open avenues for future research aimed at elucidating the complex interplay between inflammation, immune responses, and CRC pathogenesis.

CONCLUSION

In summary, the observed modulation in cytokine response among individuals with colorectal carcinoma implicates a contributory role in shaping the tumor milieu and related inflammatory mechanisms integral to CRC advancement. This aberrant cytokine profile serves as a prospective target for therapeutic interventions aimed at modulating the immune responsiveness in colorectal carcinoma patients.

6. Declarations

Conflict of interest
The authors have no conflicts of interest to declare.

Funding
This work was financially supported by the Russian Science Foundation (Grant number 25-25-00358).

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