Brief Report

Autophagy Dysregulation in Crohn's Disease and Colorectal Cancer—An Analysis of *BECN1*, *PINK1*, and *LAMP2* Gene Expression

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Autophagy Dysregulation in Crohn's Disease and Colorectal Cancer—An Analysis of *BECN1*, *PINK1*, and *LAMP2* Gene Expression

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Abstract

Crohn's disease (CD) and colorectal cancer (CRC) are clinically distinct but pathogenetically related conditions in which significant abnormalities in autophagy are observed. The aim of the study was to evaluate the expression of three key autophagy-related genes, i.e., *BECN1* (macroautophagy), *PINK1* (mitophagy) and *LAMP2* (chaperone-mediated autophagy) in tissue samples from patients with CD and CRC. The study material included samples from 48 patients with CD (n = 96 biopsy samples) and 87 patients with CRC (n = 87 tumors; n = 87 normal paired controls). Transcriptomic analyses were performed using Affymetrix HG-U133A microarrays. They were confirmed by RT-qPCR. The Kruskal-Wallis test with Dunn's post hoc analysis ($\alpha = 0.05$) and Spearman's correlation coefficients were used for statistical evaluation. Expression of *BECN1* and *LAMP2* was significantly decreased in both CD and CRC compared to the controls ($p = 0.009$; $p = 0.023$, respectively). However, *PINK1* showed significantly higher expression levels in CD compared to CRC and the controls ($p < 0.001$). The clinical stages of CRC (I-IV) did not significantly affect the expression of the analyzed genes. The study findings confirm the presence of common abnormalities in autophagy in CD and CRC with decreased macroautophagy and chaperone-mediated autophagy with the compensatory activation of mitophagy. *BECN1*, *PINK1* and *LAMP2* expressions may have a diagnostic and therapeutic value in the context of chronic inflammation and colorectal carcinogenesis.

Keywords: autophagy; Crohn's disease; colorectal cancer; *LAMP2*; *PINK1*; *BECN1*

1. Introduction.

Crohn's disease (CD) is a chronic autoimmune inflammatory disease of the gastrointestinal tract with increasing incidence worldwide. Together with ulcerative colitis (UC) and indeterminate colitis, it is classified as inflammatory bowel disease (IBD), which has a confirmed impact on the risk of colorectal carcinogenesis. In these patients, the risk of colorectal cancer (CRC) is twice as high as in the general population. Furthermore, CRC is the leading cause of death in patients with IBD and accounts for about 15% of all deaths in individuals with IBD [1–3]. Patients with IBD have a 2% risk

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of CRC, which is 5 to 15-fold higher than the risk in the general population over 30 years [4]. Additionally, patients with primary biliary cholangitis are slightly more likely to have CRC [5].

Crohn's disease can affect any segment of the gastrointestinal tract. Compared to UC, the lesions are discontinuous, affecting the entire intestinal wall. Active CD increases the risk of mucosal dysplasia, and one-third of patients with CRC develop synchronous tumors or dysplasia in distant locations during the course of the disease [6,7].

Patients with colorectal CD have a relative risk of CRC of 2.5, and a cumulative risk of CRC at 10 years is 2.9%. The tumor location depends on the localization and intensity of inflammatory changes in the section of the gastrointestinal tract [8]. In addition to CRC, patients with CD have a higher risk of other cancers of the gastrointestinal tract (e.g., gastric cancer, cholangiocarcinoma, liver cancer) and extraintestinal cancers such as lymphoma and skin cancer, which is due to the inflammatory background of the disease and the drugs used to treat the condition [9,10].

Autophagy is one of the primary mechanisms of cellular homeostasis and occurs by recycling damaged proteins and organelles and older or misfolded proteins [11]. The levels of autophagy can be impaired depending on various factors, such as inflammatory diseases and cancer [12]. It seems that autophagy can be both "an enemy and ally" of cancer, depending on pathological or physiological conditions [13]. This appears to be associated with autophagy (macroautophagy, microautophagy, selective autophagy, chaperone-mediated autophagy) [14]. Macroautophagy is a process consisting of several stages in which the *BECN1* protein is responsible for the formation of the phagophore, which leads to the formation of the autophagosome. In turn, the *PINK1* protein is involved in lysosomal mitochondrial degradation in selective autophagy (mitophagy), and the *LAMP2* protein is involved in chaperone-mediated autophagy (CMA) regulation also known as CD107b (Cluster of Differentiation 107b) and Mac-3, is a human gene [14]. Understanding these mechanisms opens new therapeutic possibilities [15].

The aim of the study was to investigate the potential relationship between autophagy dysregulation in patients with CD and those with colorectal cancer. Specifically, we compared the expression of genes encoding key autophagy-related proteins (*BECN1, PINK1* and *LAMP2*) to identify similarities or differences in transcriptional activity between the two patient groups. The analysis of gene expression levels may provide insights into the shared molecular mechanisms underlying impaired autophagy in chronic intestinal inflammation and tumorigenesis. Our findings may contribute to a better understanding of the dual role of autophagy in IBD and colorectal cancer development.

2. Results and Discussion

The study included 135 patients (aged 38 to 83 years), 87 of whom underwent elective surgery for CRC at different clinical stages of the disease and 48 patients diagnosed with CD.

In the first step, the basic descriptive statistics for *BECN1*, *PINK1* and *LAMP2* gene expressions were compared in three groups: CD, CRC and CT.

The medians for *BECN1* and *LAMP2* in the CD and CRC groups were lower than in the control group. On the other hand, *PINK1* had a very high median expression in patients with CD. A significantly lower median expression of *PINK1* was reported in the group of patients with CRC, which was also higher than in the CT. The clinical characteristics of the study group with CD and CRC are given in (Tables 1-3).

Table 1. Clinical characteristics of patients with CD and CRC.

Parameter	CD group N = 48				CRC group N = 87				p
	Median	Range	Q1	Q3	Median	Range	Q1	Q3	
Age [y]	43.5	22-78	31.0	58.5	68.0	41-82	59.0	73.0	0.0001
Height [m]	1.70	1.54-1.94	1.63	1.77	1.66	1.54-1.88	1.56	1.76	n.s
Body mass [kg]	62.0	35-107	56.5	72.5	76.0	45-105	63.0	87.0	0.0001

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BMI (kg/m²)	21.85	13.5-28.43	19.42	24.20	26.45	18.17-36.73	24.45	29.50	0.0001
Ht [%]	36.1	25.1-47.4	30.4	40.5	37.9	27.2-47.8	36.2	40.1	n.s
WBC [M]	7.12	3.60 -25.1	4.84	9.67	6.56	2.90-15.76	5.09	8.37	n.s

N—number of patients; BMI—Body mass index; Ht—hematocrit; WBC—white blood cell count, Q1/Q3—lower quartile/upper quartile; p—level of statistical significance; n.s.—not statistically significant.

Table 2. Distribution of patients by gender.

Gender	CD group		CRC group		p
	N	%	N	%	
Female	28	58.0	36	41.4	n.s.
Male	20	42.0	51	58.6	n.s.

N—number of patients; p—level of statistical significance; n.s.—not statistically significant.

Table 3. Analysis of the incidence of cancer stage in patients with CRC.

Cancer stage	Number of cases	%
Stage I	22	25.3
Stage II	20	23.0
Stage III	33	37.9
Stage IV	12	13.8
Total	87	100.0

Table 4, shows the descriptive statistics for *BECN1*, *PINK1* and *LAMP2* in the analyzed groups.

Table 4. Comparison of gene expression in the CD, CRC, and control samples using Kruskal-Wallis H test.

Gene/group patients		N	Mean rank	Median	Q1	Q3	H	P	η2	post hoc a
				mRNA copy/µg RNA						
BECN1	CD	96	121.511	4062.000	280.500	16890.000	9.421	0.01	0.030	CD vs CT
	CRC	87	132.823	6388.000	1571.000	13100.000				
	CT	87	156.433	10560.000	3853.000	20385.000				
PINK1	CD	96	197.411	17380.000	5929.000	21952.000	89.920	<0.001	0.320	CD vs CRC CD vs CT
	CRC	87	119.332	194.000	0.571	7199.000				
	CT	87	91.701	13.201	0.073	1292.000				
LAMP2	CD	96	126.900	19215.000	4596.500	24650.000	7.540	0.02	0.020	CRC vs CT
	CRC	87	122.500	18250.000	10770.000	29310.000				
	CT	87	151.702	34135.000	14357.500	51742.500				

N—number of patients; Q1/Q3—lower quartile/ upper quartile; p—level of statistical significance; post hoc a—pairs for which post hoc differences were significant at $p < 0.05$. *H*—Kruskal-Wallis H test; η^2—eta squared (effect size measure).

The Kruskal Wallis H test was performed to compare the results of patients with CD and CRC with the controls. The analysis showed significant differences in the values of genes between the groups. To determine the differences between the compared groups, Dunn's post hoc pairwise

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comparisons test with a Bonferroni correction was applied (Table 4). Significantly higher levels of *BECN1* were found compared to the CT ($p = 0.009$). Samples of patients with CD showed higher levels of *PINK1* compared to those with CRC and the controls. Significantly lower levels of *LAMP2* were found in CRC samples compared to the controls. Other differences between the groups were non-significant.

In addition, correlation analysis was performed between the expressions of the three genes using Spearman correlation analysis. In the whole sample, a weak but statistically significant positive correlation was observed between *LAMP2* and *PINK1* ($r = 0.16$, $p < 0.01$), while *PINK1* and *BECN1* were negatively correlated ($r = –0.23$, $p < 0.01$). No significant correlation was found between *LAMP2* and *BECN1* in this group. No statistically significant correlations were detected between the analysed genes in patients with CD. In the CRC group, *LAMP2* and *PINK1* showed a moderate positive correlation ($r = 0.28$, $p < 0.01$), whereas *PINK1* and *BECN1* were inversely correlated ($r = –0.24$, $p < 0.05$). The correlation between *LAMP2* and *BECN1* was not significant. Interestingly, a strong positive correlation was found between *LAMP2* and *PINK1* ($r = 0.51$, $p < 0.01$) in the control group, which was the most pronounced among all subgroups. No significant correlations were reported between *BECN1* and the other two genes in this group.

Subsequently, the Kruskal Wallis H test was performed to compare gene expression among samples with different stages of colon cancer (CSI, CSII, CSIII and CSIV), For *BECN1*, the median expression decreased progressively from stage I (10245 mRNA copies/µg) to stage IV (2629 mRNA copies/µg), which suggests a potential downregulation in advanced disease. However, this trend did not reach statistical significance ($p = 0.240$). In contrast, *PINK1* expression showed a non-linear increase, with the highest median found in stage IV (7203mRNA copies/µg) and the lowest in stage I (1.4mRNA copies/µg). The difference was not statistically significant ($p = 0.196$). For *LAMP2*, a gradual increase in expression was noted from stage I (14735 mRNA copies/µg) to stage III (19830 mRNA copies/µg) to decrease in stage IV to 17775 mRNA copies/µg. Again, the differences between the groups were not statistically significant ($p = 0.602$). Overall, the analysis suggests that although slight trends in gene expression across tumor stages could exist, these differences were not statistically or biologically significant in the cohort.

The pathogenesis of CRC and IBD is poorly understood. Both genetic and environmental factors are involved. Mutations, genetic instability, epigenetic changes, impaired immune response by mucosal inflammatory mediators, oxidative stress and intestinal microbiota are thought to be responsible for CRC and IBD [16,17].

Abnormal autophagy processes are also observed in both CRC and CD. However, their roles in the pathogenesis of these conditions are different. In both cases, autophagy disorders result from or lead to exacerbation of the disease. In CD, autophagy generally has a protective function since it maintains cellular homeostasis and limits excessive inflammatory response [17–22]. Ineffective autophagy results in uncontrolled inflammation, damage to the intestinal barrier, and disease progression, as confirmed by genetic studies indicating that polymorphisms in autophagy genes (e.g., *ATG16L1*, *IRGM*, *NOD 2*) correlate with increased susceptibility to CD [17–22].

In turn, altered autophagy and chronic inflammation in CRC may promote neoplastic transformation by changing the inflammatory or immunosuppressive tumor microenvironment [18,19]. Accumulation of damaged organelles, proteins and toxic metabolites in intestinal epithelial cells promotes induction of oxidative stress and DNA damage. Furthermore, in tumor-transformed cells, dysregulation of autophagy may enhance their ability to survive under unfavorable conditions (e.g., limited nutrient availability) and can affect resistance to anticancer treatment [20].

In this respect, the aim of normal autophagy is to protect the body from excessive DNA damage, which directly contributes to the inhibition of carcinogenesis. Cells affected by chronic inflammation can inhibit one of the major cell proliferation pathways (mTOR). Its inhibition is a stimulus for the activation of autophagy processes aimed at degrading damaged cells, thereby preventing their potential malignant transformation [20].

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3. Materials and Methods

3.1. Patients and Methods

3.1.1. Study Design

The study included 135 patients (aged 38 to 83 years), 87 of whom underwent elective surgery for CRC at different clinical stages of the disease and 48 patients diagnosed with CD. In patients with CD, the Crohn's Disease Activity Index (CDAI) was determined (median 188, range 74-446). Clinical characteristics did not differ significantly between the study groups in terms of parameters such as gender, height, hematocrit, and white blood cell count. Statistically significant differences were observed between the CRC and CD groups in terms of age (68 vs. 43.5 years, respectively) and BMI (26.5 vs. 21.9, respectively).

In the CRC group, the percentage of patients with particular clinical stages was as follows: I—25.3%, II—23.0%, III—37.9%, and IV—13.8%. The inclusion criteria for patients with CD and CRC were as follows: age > 18 years, any stage of disease progression and written informed consent to participate in the study (**KB SUM No. KNW/0022/KB1/21/I/10**).

The exclusion criteria included: severe systemic or metabolic conditions (except for obesity as an isolated disorder), a history of radio- or chemotherapy, other malignant conditions, active or a history of chronic inflammatory conditions, including IBD in patients with CRC and second surgery for the underlying disease.

Tumor and healthy control tissue samples were obtained during classical surgical resection of the colon due to cancer. The material consisted of 87 tumor samples (CRC group) and 87 healthy tissue samples obtained from an area at least 5 cm outside the histologically negative margin served as the control group, (CT). Cancer samples were obtained from the peripheral regions of the tumor to exclude the presence of necrotic tissue.

To minimize sampling errors in all 48 patients with CD, the samples were obtained from two locations of the most severe intestinal inflammatory lesions by the same surgical team. Eighty-six samples of the affected tissue were taken from 43 patient during a colonoscopy and 10 samples from 5 patients undergoing elective surgery for (sub)ileus or internal fistula (CD group, n = 96 samples in total). In patients with CD, two samples of affected tissue were collected due to the difficulties in precise determining the location of the most severe intestinal inflammatory lesions during the endoscopic examination and blurring of the macroscopic boundaries between healthy and affected tissue, which resulted in obtaining twice as many results than the real number of patients in the group. Immediately after the excision of the colonic segment or endoscopic biopsy collection, the material was placed in sterile tubes containing RNA *later*™ (Sigma) in the amount of 10 µL per 1 mg of tissue (200 µL RNA *later*™ per 20 mg of tissue). The samples were stored for 24 h at 4 °C. Next, the sections were frozen at -80 °C until further analysis. Molecular studies were performed at the Department of Molecular Biology of the Medical University of Silesia.

The first step of laboratory procedure was to isolate the total RNA using an electric homogenizer (Kinematica AG, Bern, Switzerland). The RNA was isolated according to the manufacturer's instructions using the TRIzol® reagent (Life Technologies, Carlsbad, CA, USA) and was purified with the Qiagen RNeasy Mini Kit (Qiagen, Hilden, Germany) in combination with DNase I digestion. The Gene Quant II (Pharmacia Biotech, Uppsala, Sweden) spectrophotometer was used to quantify the RNA using an absorbance of 260 nm.

Confirmation of the results of the comparative analysis of transcriptomes determined by the expression microarray technique was carried out using the RT-qPCR method, which is considered the gold standard in the validation of matrix experiments. The results of the transcriptional activity analysis are given as the number of mRNA copies per 1 µg of total RNA.

The expression of *BECN1*, *PINK1* and *LAMP* genes involved in ubiquitin-mediated protein degradation was investigated by RT-qPCR reaction.

The thermal profile of the RT-qPCR reaction included the following steps: reverse transcription (45ºC for 10 minutes), polymerase activation (95ºC for 2 minutes), 40 cycles including denaturation

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(95ºC for 5 seconds), primer attachment (60ºC for 10 seconds) and elongation (72ºC for 5 seconds). The reaction was performed using specific primer pairs for each gene (Sigma-Aldrich, St Louis, MO, USA).

The investigated genes expression was calculated based on the standard curve prepared for commercially available DNA templates of the β-actin gene using the TaqMan DNA Template Reagent (PE Applied Biosystems). Microarray analysis was validated with qRT-PCR. The transcriptional activity of genes involved in autophagy in CD and CRC was investigated and compared to the normal tissues (controls).

3.1.2. Statistical Analysis

The statistical significance of the differences in transcriptional activity of the genes involved in autophagy ($p < 0.05$) was evaluated by comparative analysis of RT-qPCR results performed using Data Analysis Fundamentals software (Affymetrix Inc., USA), Gene Spring GX 11.5 software (Agilent Technologies) and IBM SPSS Statistics 26.0 (StatSoft, Tulsa, OK, USA). The results were normalized using the RMA software and the Gene Spring GX 11.5 software, which enabled the selection of genes differentiating transcriptomes depending on the stage of progression of adenocarcinoma.

For each parameter, the most essential elements of descriptive statistics were determined (i.e., mean, median, standard deviation, and upper [75%] and lower [25%] quartiles).

Statistical tests were performed using the Kruskal Wallis H method to compare the groups in terms of the variables. The Dunn test with a Bonferroni correction was used for post hoc analysis. The level of significance was $\alpha = 0.05$.

3.1.3. Bioethical Consent

The study received the consent of the Medical University of Silesia (KB SUM No. KNW/0022/KB1/21/I/10). All authors committed to complying with the ethical principles of clinical research based on the Declaration of Helsinki.

3.1.4. Limitations of the Study

This study has several limitations. Firstly, expression analysis was limited to the mRNA level (qPCR) without simultaneous assessment of functional autophagy activity such as LC3 or p62 protein levels and autophagosome flux dynamics. Secondly, the lack of longitudinal data makes it impossible to assess changes in autophagy gene expression over time, particularly during the transition from CD to CD-CRC, which limits the ability to identify these genes as early markers of tumor transformation. In addition, translation and protein expression levels were not assessed, which is a significant limitation since a decrease in mRNA levels is not necessarily directly associated with a decrease in functional protein levels. Furthermore, the study groups differed in terms of age, weight and BMI due to their different clinical nature. However, these variables should not significantly affect the results of the analysis.

4. Conclusions

Autophagy pathways have been reported to be significantly impaired in the pathogenesis of CD and CRC. Their interrelation plays a key role in maintaining cellular homeostasis under stress conditions leading to an immune response dependent on changes in the microenvironment and disease stage.

The study findings indicate that *BECN-1* dependent macroautophagy in CRC may have a protective function at the early stage of tumor development, maintaining its anti-oncogenic properties, which are decreased or deactivated as the disease progresses. In CD, macroautophagy is activated as a protective mechanism in response to chronic inflammation. However, its dysregulation during carcinogenesis in patients with CD may contribute to the development of a more aggressive form of colorectal cancer, which is associated with a poorer prognosis and higher mortality.

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Decreased expression of the *BECN1* gene found in CD and CRC may indicate common mechanisms of macroautophagy dysfunction underlying inflammation-induced carcinogenesis in the large intestine. However, increased *PINK1* expression in CD indicates activation of protective mitophagy mechanisms in response to chronic inflammation. The importance of mitophagy in CRC increases in correlation with a decrease in the efficiency of macroautophagy at crucial stages of tumor progression (CSII, CSIV).

The decrease in *LAMP2* activity in CRC and CD indicates the inhibition of the CMA pathway in CRC. In CRC, such inhibition may represent an adaptive tumor mechanism to chronic metabolic or oxidative stress, which allows temporary tolerance of damaged proteins. This phenomenon may promote the survival and proliferation of cancer cells, thus contributing to their growth under stress conditions. Significantly differentiated changes in *LAMP2* activity in CD suggest its usefulness as a marker for assessing CD activity.

A strong positive correlation between *PINK1* and *LAMP2* in healthy tissues, which was not found in CD or CRC, indicates a profound dysregulation of mechanisms of cell quality control under pathological conditions**.**

Understanding the dynamically changing role of autophagy in CD and large intestine carcinogenesis has essential implications for discovering new therapeutic strategies and markers for these diseases. Our findings support the potential usefulness of *BECN1*, *PINK1* and *LAMP2* as biomarkers or therapeutic targets in CRC and CD and encourage continued research.

Author Contributions: MBL, DW, PK and MMW conceived the concept of the study. All authors contributed to the design of the research. **MBL:** DW, PK, MŚ, MK, MB, MMW were involved in data collection. DW, MBL, PK, analysed the data. MBL, DW, PK, MŚ, MK, MB, MMW wrote the manuscript. DW, PK MBL, MŚ, MK, MB, MMW critically revised the article. DW coordinated funding for the project. All authors edited and approved the final version of the manuscript.

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Abbreviations

(CD)	Crohn's disease
(UC)	ulcerative colitis
(IBD)	inflammatory bowel disease
(CRC)	colorectal cancer
BECN1	the human gene encoding the Beclin-1 protein
PINK1—PTEN	*induced kinase 1*
LAMP2	Lysosome-associated membrane protein 2
(CMA)	chaperone-mediated autophagy
(CSI, CSII, CSIII and CSIV)	different stages of colon cancer
(mTOR)	major cell proliferation pathways
CD107b)	Cluster of Differentiation 107b

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