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## Effect of TLRs and nuclear PPAR $\gamma$ receptors on the mechanisms of intestinal carcinogenesis

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**Abstract:** Toll Like Receptors (TLR) are transmembrane proteins that play an important role in immune reactions associated with the recognition of pathogenic factors that cause infection.

However, chronic inflammatory conditions associated with the activation of these receptors create favorable conditions for the development of cancerous processes. The relationship between nuclear PPAR $\gamma$  receptors and TLR receptors is also important, whose role and importance in the process of carcinogenesis is the subject of various studies.

**Key words:** Toll Like Receptors (TLR), peroxisome proliferator-activated receptors (PPARs), carcinogenesis, cyclooxygenase 2 (COX-2).

### Introduction

The mammalian immune system recognizes pathogens due to the presence of TLR (Toll Like Receptors). TLR (Toll Like Receptors) are members of the PRR family (Pattern Recognition Receptors) and are present on the surface of APC (Antigen Presenting Cells) cells — macrophages or dendritic cells [1, 2]. These receptors recognize specific molecular patterns (PAMPs) associated with pathogens, as well as those released from dead cells (DAMPs) [3].

The human intestinal flora is composed of many different species of microorganisms and due to the host's immune tolerance determines the existence of homeostasis. Disorder of this homeostasis may cause chronic inflammation caused by autoimmune diseases or bacterial infections and is a significant risk factor in the development of gastrointestinal tumors [4, 5]. Long-term, continuous bacterial stimulation with LPS endotoxin therefore modulates TLR functions causing changes in the expression and signaling of these receptors [6–8]. PAMP molecules reacting directly with TLR receptors may thus significantly support the process of carcinogenesis [9, 10]. In addition, the relationship between nuclear PPAR $\gamma$  receptors with a proven function blocking the progression of intestinal carcinogenesis and TLRs is also important. The above interaction seems to play an important role due to the fact that PPAR $\gamma$  belong to the group of TLR receptor inhibitors [11].

### **Intestinal carcinogenesis**

Carcinogenesis is a process leading to the formation of cancer, which in many cases can be described as an acquired genetic disease. At the basis of carcinogenesis lies the dysfunctions of gene function, as tumors arise as a result of a series of germinal and / or somatic DNA mutations [12, 13].

Pre-cancerous conditions include: single adenomas, non-specific inflammatory bowel diseases and familial polyposis syndromes. Most sporadic cancers develop due to mutations in suppressor genes, such as APC, DCC, and p53. As a result of these mutations, glandular epithelium and adenoma develop [14, 13]. The next step is the transformation of a malignant adenoma as a result of the inactivation of oncogenes, K-ras [14]. In addition, in the case of hereditary Non-Polyposis Colorectal Cancer (HNPCC), the carcinogenesis process is carried out by inactivating the repair genes that are responsible for the genetic stability of the cells. Mutations of these genes lead to uncontrolled proliferation of the intestinal epithelium [15]. The symptom of the above disorders is microsatellite instability, which is observed in 100% HNPCC and in 15% of cases of sporadic cancer [16]. Another pathway for the transformation of normal epithelium into cancerous is the mechanism that causes functional exclusion of genes and hyper methylation of genes in the regions of promotor genes: hMLH1, APC and p16 [17].

Colorectal cancer is the second cause of death from malignant tumors. Both the incidence and mortality due to this cancer systematically increases in the European population [18]. Differences in the epidemiology of bowel cancer result from environmental factors, the most important of which is the diet. A diet rich in animal fats, low in calcium and selenium has a negative effect on intestinal flora, increases the time of passage of the food content and induces the synthesis of precursors of carcinogenic compounds [19]. Prognosis in colon cancer depends mainly on the

stage of cancer. The average 5-year survival in Poland is only 25% (the average 5-year survival in the USA is 45%) [20].

It has been proven that the prognosis for survival of colorectal cancer patients can be improved by screening in an asymptomatic population. Currently, screening consists of using one of three methods: fecal occult blood test, sigmoidoscopy and full colonoscopy. None of the above methods, however, is characterized by 100% sensitivity and specificity in the detection of neoplastic lesions, therefore there is a strong need to develop widely available methods based on easy to implement, as little invasive and sensitive techniques of molecular biology [21, 22].

### **The role of Toll-like receptors (TLRs) and PPAR $\gamma$ in the carcinogenesis process**

Toll-like receptors (TLRs) have the effect that the innate immune system recognizes specific molecular microbial patterns and translates them into endogenous threat signals [23, 24]. Under homeostasis conditions, host proteins known as Toll Like Receptors (TLRs) recognize unique microbial structures in the body, called pathogenic molecular species (PAMP). Diagnosis of PAMP activates numerous pro-inflammatory responses, which ultimately leads to the formation of acquired immunity [25]. TLR2 and TLR4 recognize lipopolysaccharides derived from exogenous microorganisms and are found mainly on the cell membrane [26, 23], whereas TLR9 recognizes viral and bacterial unmethylated CpG-DNA and is usually located intracellularly [27, 23].

Toll Like Receptors (TLRs) are among the transmembrane receptor proteins expressed on the cell membrane as well as on the endosomal membrane. The TLR family is generally characterized by the presence of leucine-rich repeats and the Toll / interleukin-1 domain, which mediates ligand binding and interaction with intracellular signaling proteins [28, 29]. Most of the TLR ligands identified so far are conservative microbiological products that signal the presence of infection, but evidence of some endogenous ligands that may signal other dangers has also been reported [28].

The involvement of TLR in carcinogenesis becomes unquestionable. TLRs recognize molecular patterns (DAMP) released into the system by tissue damage [30, 29]. Chronic activation of TLRs creates favorable conditions for the development of cancer due to pro-inflammatory reactions [31]. This leads to the strengthening of anti-apoptotic and proliferative properties of the micro environment and the formation of cancer cells [32, 23].

Peroxisome proliferator-activated receptors (PPARs) are transcription factors that belong to the family of nuclear hormone receptors. The subfamily of nuclear receptors includes retinoic acid receptors (RARs), thyroid hormone (TR) receptors and steroid receptors [33, 34]. The PPAR family contains PPAR $\alpha$ , PPAR $\gamma$  and PPAR $\delta$

receptors that perform various functions in the development of tumors. PPAR receptors were usually studied in the context of cells of the liver parenchyma where they are highly expressed [34]. PPAR functions are control of fatty acid metabolism, participation in adipogenesis — processes of cell proliferation and differentiation of adipose tissue. They are also responsible for the maintenance of glucose homeostasis, and act as a transcription factor, inhibiting the transcription of proinflammatory cytokines [35–37]. They also affect proliferation, cell differentiation by regulating gene transcription. They promote cell differentiation, have anti-proliferative activity and inhibit angiogenesis. All these processes lead to slow tumor progression [38–40].

PPARs are activated by endogenous or synthetic ligands may regulate tumor progression depending on the conditions. The activators of nuclear receptors are compounds of natural or synthetic origin [41, 36]. PPAR synthetic agonists are drugs sensitizing peripheral tissues to insulin, known as thiazolidinedione (TZD) [42–44]. These compounds include: pioglitazone, rosiglitazone, ciglitazone, darglitazone, englitazone, netoglitazone, rivoglitazone, troglitazone.

Other ligands for PPAR- $\gamma$  are prostaglandins, arachidonic acid and fatty acids or their derivative [45, 44, 43]. The nuclear receptors depend on the ligand. Full transactivation of these receptors requires dimerization of the PPAR receptor to the retinoid receptor (RXR), which induces the expression of target genes [36].

The function of PPAR- $\gamma$  receptors in the intestinal epithelium has not been fully elucidated. Current research suggests that these receptors may be an attractive target for cancer therapy. There are studies that show anti-proliferative activity and inhibit angiogenesis, which slows down tumor progression [46].

### Correlation between TLRs and cyclooxygenase 2 (COX-2) in mechanisms of intestinal carcinogenesis process

The importance of TLRs in the pathogenesis of colorectal cancer is the subject of numerous studies of recent years [47]. It was observed that changes in the expression of TLRs on tumor cells initiate a signaling path activating the kinase cascade, NF- $\kappa$ B, and the production of antiapoptotic proteins that contribute to the development of cancer and cancer cell proliferation [48, 49].

They also promote the production of cytokines and chemokines that recruit cells of the immune system to increase resistance to tumor microenvironment [50, 51]. Optimized immune cells release pro-inflammatory cytokines, growth-promoting proangiogenic factors that may impair the antitumor function of APC cells and effector T cells [2]. Activation of TLR-4 depends on the MyD88 adapter protein. Rakoff-Nahoum and colleagues have shown that the TLR/MyD88 signaling pathway is involved in tumor progression in APC<sup>Min</sup> mice in the familial polyposis model, thereby proving the involvement of the intestinal flora in carcinogenesis [52, 53].

There is a clear link between TLR-4 signaling and COX-2 expression in the gut. Prolonged TLR-4 receptor stimulation with bacterial endotoxin contributes to increased activation of inflammatory factors, including increased transcription of COX-2, which causes persistence of inflammation and has a carcinogenic effect [50].

Cyclooxygenase 2 is an enzyme that catalyzes the transformation of arachidonic acid. COX-2 overexpression was found in tumors of the large intestine, stomach or pancreas. The enzyme is involved in many processes leading to the development of cancer. Increased expression of COX-2 inhibits apoptosis by increasing the activity of anti-apoptotic proteins (BCL-2) and activation of the serotonin-threonine kinase (Akt) pathway [50, 3]. In addition, COX-2 expression contributes to the initiation of neoangiogenesis (vasculogenesis and growth), as well as to the increase in metalloproteinase activity which has a direct effect on infiltration and spread by metastasis. In addition, COX-2 also weakens the activity of the immune system by disturbing the balance between IL-10 and IL-12, which leads to immunosuppression and intensification of angiogenesis [3].

The increase in TLR-2 and TLR-4 expression has been observed on many colon cancer cell lines as well as in stomach tumors. The increase in receptor expression seems to be regulated there by the commensal flora that colonizes the intestinal lumen or by colonization with *H. pylori* strains of the stomach environment [54, 3]. It was also noted that TLR-4 is overexpressed in colorectal cancer cells from patients with intestinal inflammation, as well as in colorectal cancer cells in the mouse colitis model. Grishin *et al.* Have recently shown that LPS stimulates COX-2 in the rat's intestinal epithelial cell line, which may play an important role in necrotizing enterocolitis [55, 56]. Cancer cells of the stomach cancer express several types of TLR, which enables interception with *H. pylori* strains or other microorganisms. Also in people suffering from IBD (inflammatory bowel disease) in the intestinal mucosa, TLR-2, TLR-4 is overexpressed especially during the persistence of inflammation [54].

On the one hand, TLR mediates carcinogenesis through regulation of the NF- $\kappa$ B pathway and antiapoptotic effect, on the other hand expressed in tumor cells TLRs and tumor growth seem to favor PAMP (LPS) and persistent chronic inflammation. Therefore, the search for strategies aimed at suppressing TLR4 signaling can significantly reduce the chronic inflammatory process that promotes carcinogenesis [56, 50, 3].

### Correlation between TLR and PPAR $\gamma$ in the mechanisms of intestinal carcinogenesis

PPAR $\gamma$  functions in the intestinal epithelium have not been fully elucidated. Current research suggests that these receptors may be the target of anti-cancer therapy and also have anti-inflammatory properties. These receptors are important in inhibiting

the signal path activating the NF- $\kappa$ B nuclear factor cascade. Ligands of these receptors are described as growth inhibitors and promote apoptotic processes of cancer cells [57, 58]. Increased expression of PPAR $\gamma$  receptors in the colon epithelium and in large intestine cells has been demonstrated, where they play a potential role in regulating inflammation. Activation of PPAR $\gamma$  inhibits mucosal production of inflammatory cytokines (TNF $\alpha$ , IL-1 $\beta$ ) by a decrease in NF- $\kappa$ B nuclear factor activity and MAP protein kinases [59, 58].

PPAR $\gamma$  receptors are activated by several ligands. Current studies show that the role of agonists in these receptors is played by 15dPGJ2 (15deoxy $\Delta^{12,14}$  prostaglandin) and thiazolidinedione derivatives (thioglitazone) — insulin sensitizers and used to treat diabetes [44]. It was noted that in precancerous and neoplastic conditions the expression of TLR increases and the activity of PPAR $\gamma$  receptors decreases. In studies of suppression of inflammation by PPAR $\gamma$  in IEC after stimulation with HT-29 endotoxin LPS, an increase in the activity of proinflammatory cytokines (COX-2, IL-8) was observed [59, 11]. On the other hand, after stimulation of the PPAR $\gamma$  receptors with the 15dPGJ2 ligand, the LPS induction and decreasing cytokine expression were attenuated. These results are consistent with the results of other studies carried out in intestinal models and showing the inhibitory effect of PPAR $\gamma$  ligands on inflammatory processes [11]. The action of ligand on PPAR $\gamma$  weakens TLR-4 induced endotoxin, which may suggest an interaction between inflammatory TLRs and the PPAR $\gamma$  non-inflammatory pathway [59, 11]. PPAR $\gamma$  ligands may thus affect TLR-4 signaling pathways directly through PPAR $\gamma$  signaling in epithelial cells, or indirectly by anti-inflammatory effects induced by PPAR $\gamma$  receptors [60]. LPS endotoxin significantly increases the PPAR $\gamma$  activity based on which it can be concluded that TLR-4 in intestinal epithelial cells mediates the regulation of the expression of these receptors [60, 11].

PPAR $\gamma$  has also been associated with colon cancer in mice. It appears that PPAR $\gamma$  receptor ligands are involved in both promotion and the process of protection against this cancer. This is a negative target of the APC gene, which is mutated in familial adenomatous polyposis, an inherited disease characterized by multiple colorectal adenomas [61, 59, 36]. In addition, the non-steroidal anti-inflammatory drug (NSAID) sulindac, which inhibits the formation of colorectal tumors, may antagonize PPAR $\gamma$ . Therefore, PPAR $\gamma$  may be a critical intermediate in the carcinogenic pathway of the APC gene and be a molecular target for the action of NSAIDs on colorectal cancer [36].

There are also reports indicating that PPAR- $\gamma$  activation promotes the development of colon cancer in APC<sup>Min</sup> mice [62, 61, 59]. These results contrast with the results of studies demonstrating the anti-cancer activity of PPAR $\gamma$  receptors. Moreover, the authors show that the overexpression of  $\beta$ -catenin as a cofactor of transcription increases the activity of PPAR $\gamma$  in colon cancer cells [63, 42]. These results are

consistent with other studies that show the relationship between  $\beta$ -catenin and nuclear receptor signaling [64, 65]. In many cells, the opposite effect of WNT/ $\beta$ -catenin and PPAR $\gamma$  is observed. Often, PPAR $\gamma$  amplification induces inhibition of the  $\beta$ -catenin pathway, whereas activation of the WNT/ $\beta$ -catenin pathway causes inactivation of PPAR $\gamma$  [63]. It was also observed that inhibition of the WNT/ $\beta$ -catenin pathway induces PPAR $\gamma$  [66].

In cancer cells, the increased regulation of WNT/ $\beta$ -catenin signaling causes changes that are conducive to cell proliferation and growth. In some studies, the protective role of PPAR gamma against cancer has also been documented [67]. In PPAR gamma colorectal cancer, it reduces oncogenic beta-catenin and inhibits cell proliferation [68].

These studies are opposite to other reported results, which show the involvement of receptors in promoting cancer development [62, 61, 59]. Therefore, the biological significance of PPAR gamma in cancer induction remains controversial and requires further research. Like the interactions of receptors with  $\beta$ -catenin.

## Conclusions

The development of the cancer process depends on the activation of specific signaling pathways and the control of cell proliferative processes. Recent studies have shown that PPAR $\gamma$  receptors have anti-proliferative activity [57, 58]. At the same time, there is a growing number of reports on the role of PPAR $\gamma$  in the promotion of intestinal carcinogenesis [62, 61, 59]. The role and importance of TLR and PPAR $\gamma$  receptors in the pathogenesis of tumors is the subject of numerous studies of recent years. However, the exact molecular mechanism is not yet fully understood.

Coexistence of chronic inflammatory processes can significantly contribute to the growth of the hyper proliferative epithelium within the intestines. The resulting changes may be the cause of cancer development. Therefore, the development of a strategy aimed at suppressing TLR signaling and weakening of the inflammatory process, as well as further research deepening knowledge about cancer therapy, the aim of which may be PPAR receptors are necessary and should be continued.

## Conflict of interest

None declared.

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