Cancer Cell Research 27 (2020) 729-735

Available at http:// www.cancercellresearch.org ISSN 2161-2609

Research progress on the prevention of colorectal cancer with Phytic Acid

Jingjing Wang, Genquan Jin, Xiubo Jiang*

School of Public Health, Qingdao University, Qingdao 266071, China

Abstract: **Phytic acid is an inositol ester containing six molecules of phosphoric acid, which is ubiquitous in plant seeds. It has various biological effects such as chelating, anti-oxidation, regulating immunity, anti-tumor, reducing inflammation, and inducing autophagy. A large number of animal and in vitro experiments have confirmed that phytic acid is a broad-spectrum anti-tumor substance that has effects on different cell and tissue systems. The number of people diagnosed with colorectal cancer each year is second only to lung cancer and breast cancer, ranking third in the world. It is a common gastrointestinal malignant tumor in my country. Metastasis is a key feature of malignant tumors, and it is also a difficult point in the treatment of cancer. Most treatments for colorectal cancer have side effects, and phytic acid has no obvious toxicity to normal cells. It can inhibit the metastasis of colorectal cancer, but its specific mechanism is not clear. If the mechanism of action can be clarified, it will provide a new target for the prevention and treatment of colorectal cancer. In this article, we reviewed the research progress of phytic acid and the mechanism of action of colorectal cancer metastasis.**

Keywords: Phytic acid, Transfer, Colorectal cancer, Anti-tumor

Received 8 July 2020, Revised 24 August 2020, Accepted 25 August 2020

*Corresponding Author: Xiubo Jiang, jiangxiubo2005@126.com

1. Introduction

Colorectal cancer is one of the most common malignant tumors and has the third highest incidence in the world, with 1.36 million people diagnosed with colorectal cancer each year. It is more common in Australia, Europe, North America and other countries and regions, with higher relative risk of age, sex and family history. Epidemiological studies have found that frequent consumption of red meat and processed meat products, dietary deficiencies of fruits and vegetables, overweight/obesity, smoking, and lack of physical activity increase the risk of colorectal cancer[1]. The incidence of colorectal cancer in China is increasing year by year, and the patient has the characteristics of light age of onset, low degree of differentiation, high degree of malignancy and more advanced patients[2].

In recent years, although new diagnosis and treatment technologies and chemotherapy drugs have been constantly updated, greatly improving the therapeutic effect of colorectal cancer patients, the overall survival rate of patients has not significantly improved. The main reason is that most of the patients with colorectal cancer in radical surgery before micrometastases already appeared, and colorectal cancer in our country colorectal cancer caused by high transfer rate is late[3]. Therefore, tumor metastasis has become a key link in the prevention and treatment of colorectal cancer. However, the lack of in-depth understanding of the mechanism of colorectal cancer metastasis hinders the timely adoption of effective measures to prevent and treat tumor invasion and metastasis. Recent research on the mechanisms of tumor metastasis has made encouraging progress and led to the exploration of new prevention and treatment strategies[4]. Dietary deficiencies of fruits and vegetables, overweight/obesity, smoking, lack of physical activity and other factors can increase the risk of colorectal cancer[1]. The incidence of colorectal cancer is on the rise in some low-incidence areas of Asia, which is closely related to the western diet.

An increase in dietary fiber intake of wheat bran, grains and beans may reduce the risk of colorectal cancer. Studies have found that phytic acid in dietary fiber actually plays an anti-tumor role[5]. Phytic acid is also known as phytic acid, widely exists in nature, is a highly active pure natural compound, its molecular formula is C6H18O24P6, molecular weight is 660.8, it consists of a six ring and inositol phosphate groups, strong acid, soluble in water, mainly exists in grains, beans and seed, phytic acid can under certain conditions to take off one, two, three, four, five, six phosphate groups, and get the second level phosphorylation forms. Phytic acid and its secondary phosphorylation form are in high content in mammalian cells which has a variety of biological effects, such as chelation, anti-oxidation, regulation of immunity, anti-tumor, reduction of inflammation and induction of autophagy[6]. Phytic acid is generally obtained from rice bran by ion exchange. Its toxicity is lower than that of table salt. It is safe and non-toxic as

a food additive. Some clinical studies have shown that phytic acid can enhance the effect of chemotherapy drugs and will greatly reduce side effects in patients with breast or colon cancer. A daily intake of 1 to 2 grams of phytic acid may prevent the development of cancer, while an intake of 8 to 12 grams per day may be used for anti-tumor therapy. Therefore, ensuring phytic acid intake is important for the prevention of colorectal cancer.

2. The function of phytic acid in absorption and metabolism in vivo

Phytic acid can form insoluble complexes with minerals, proteins, enzymes and other substances. This property of phytic acid may hinder the absorption of iron, zinc, calcium and magnesium, and its inhibiting effect on mineral absorption is more obvious in people with insufficient intake of their own nutrients, deficient in minerals and their micronutrients and high nutrient requirements[7]. However, some studies have shown that phytic acid does not inhibit the bioavailability of minerals as long as the diet is balanced[8, 9]. The distinct effects of phytic acids on minerals are due to a variety of biological effects of phytic acids. Phytic acid on the surface of the daily diet of iron, zinc, calcium, magnesium and other trace elements absorption and utilization, played a role in the inhibition of absorption. In fact, in the complex intestinal environment, a variety of foods are mixed together, such as organic acids, ascorbic acids, complexing agents and some compounds produced by food fermentation, which compete with phytic acids in binding minerals[10, 11]. Therefore, phytic acid has little complexation effect on minerals in a balanced diet, and there is no nutritional dietary survey to prove that phytic acid in a balanced diet will affect mineral absorption[12].

3. The metastatic mechanism of phytic acid against colorectal cancer

Tumor metastasis is a complex process, roughly tumor cells lose the original polarity, loss of intercellular adhesion factor, causes the movement and attack ability strengthen, degradation of basement membrane into circulation system (such as the circulation of the blood or lymph circulation) and live in it, with the circulatory system to distant organs, escape immune system regulation of clonal growth form metastases in it. The reasons are complex and multifaceted, which mainly includes, cancer cell adhesion factor to the fall in between the movement and attack ability enhancement, tumor cells secrete a variety of proteolytic enzymes (such as matrix metalloproteinases) destruction of extracellular matrix and basement membrane barrier benefit from, secrete a large number of angiogenic factors conducive to the formation of blood vessels, lymphatic promote tumor growth and metastasis, as well as some the inactivation of tumor suppressor genes.

3.1 Phytic acid improves the tumor microenvironment

The tumor microenvironment is the internal environment in which tumor cells are generated and live. It includes not only the tumor itself, but also the surrounding cells such as fibroblasts, immune and inflammatory cells, as well as the interstitial cells, microvessels and the biological molecules infiltrating in the nearby areas. Tumor microenvironment is closely related to the development and progression of tumor cells. Kapral et al. demonstrated that phytic acid could inhibit tumor metastasis by acting on various regulatory factors in the tumor microenvironment[13]. The antioxidant effect of phytic acid can also improve the tumor microenvironment.

An important regulator of the microenvironment, NFκB is a pre-inflammatory transcription factor. It can regulate a variety of involved cell proliferation, angiogenesis, matrix metalloproteinases. TNF- is a pro-inflammatory cytokine that may have multidirectional effects on tumor tissue because it is associated with activation of multiple signaling pathways. TNF-α cell adhesion properties and affects the concentration of soluble adhesion molecules derived from malignant colon cells[14]. IL-1β is mainly composed of activated macrophages and lymphocytes synthesis and secretion, play an important role in tumor immunity, promote transfer by induced by a variety of related factors such as matrix metalloproteinases, endothelial adhesion molecules, vascular endothelial cell growth factor and inflammatory chemokines and growth factor gene expression and promote tumor growth and metastasis. IL-6 mainly by macrophages, T cells, B cells and other tissue cells produce cytokines, is one of the important mediating factor involved in the body of tumor immune, as many kinds of tumors including colorectal cancer growth factor or paracrine growth factor to promote the proliferation of cancer cells, divided and prolong the survival of the cell, and is closely related to the cell malignant transformation and tumor progression. IL-8 is mainly produced by mononuclear macrophages, endothelial cells, hepatocytes and fibroblasts, etc. It is the first chemokine discovered. It can activate and chemotactic neutrophils and basophils. It is not only related to inflammatory response, but also closely related to tumor, and it is a multifunctional factor.

Phytic acid can adjust human colon tumor necrosis factor (TNF-α) and its receptor expression, can be elevated TNF I receptor mRNA level, and reduce the TNF alpha and II receptor mRNA expression[15], still

can reduce the promoting inflammatory molecules in the high-fat diet rats serum TNF-α and level of IL-6[16], inhibits NOS gene expression, achieve anti-inflammatory anticancer ability, cut the NFκB predominate transcriptional activity, fell to the downstream targets iNOS expression, which cut proinflammatory agent IL-β, LPS[17]. Phytic acid inhibits the transcriptional expression of inflammatory mediators IL-6 and IL-8 stimulated by IL-, elevating the expression of I B and thereby reducing the expression of P65 in the NF B family, providing anti-inflammatory effects at physiological concentrations in the gut[18, 19]. The reason may be that phytic acid inhibits the activity of P38 MAPK, leading to the decrease of IL-8 level[19]. However, in an in vitro experiment on Caco-2 cells, high concentration (5mM) of phytic acid can cause the overexpression of IL-6 and IL-6R in cells. With the increase of phytic acid dose and exposure time, Caco-2 cells continuously express higher IL-6R transcription level[19]. The results of in vitro and in vivo experiments are inconsistent, the specific reasons for which need further study.

3.2 Phytic acid can enhance the adhesion between cancer cells and prevent epithelial-mesenchymal transformation

The decreased ability of adhesion between cancer cells will also lead to the enhanced ability of movement and invasion of cancer cells. Phytic acid can regulate the cell adhesion factor between cancer cells, so as to enhance the adhesion between cells and inhibit tumor metastasis. Epithelial-mesenchymal transformation (EMT) is a biological process in which epithelial cells are transformed into mesenchymal phenotypic cells by a specific procedure. EMT is an important way for tumor cells to acquire the ability to move and invade. Reduction or loss of E-cadherin is considered to be a landmark change of tumor EMT. As a molecular marker of EMT, E-cadherin plays an important role in cell-cell adhesion and also plays an important role in invasion and metastasis of cancer cells, and is the main adhesion molecule mediating epidermal cell-cell adhesion and intercellular interactions. What E-cadherin actually sticks to between cells is a complex formed with β-catenin, and this extracellular adhesion complex is aptly described as an adhesion zipper[20]. Phytic acid can improve the colorectal cancer in the rat E-cadherin mRNA and protein levels[21], but in vitro experiments, phytic acid can reduce HT-29 cell soluble E-cadherin protein concentration, soluble cell adhesion molecules slCAM-1 mainly regulates cell adhesion, phytic acid no significant effect to the expression, to prove that the rise of soluble adhesion molecules in cells' ability to migrate to increase[14]. The results of in vitro and in vivo experiments are inconsistent and further studies are needed.

3.3 Phytic acid inhibited the adhesion between cancer cells and ECM

Phytic acid can inhibit the metastasis of cancer cells by regulating the adhesion and migration of cancer cells to the extracellular matrix (ECM). As a major component of tumor microenvironment, ECM plays a "double-edged sword" role in the process of tumor proliferation and invasion. On the one hand, ECM controls the proliferation, differentiation and metastasis of tumor cells and ACTS as a natural barrier. On the other hand, the remodeled ECM provides a loose "soil" for tumor cells to promote the occurrence and development of tumors. ECM mainly includes collagen, fibronectin and laminin. Phytic acid can reduce colorectal cancer liver metastasis in mice IV type collagen molecules, laminin and fibronectin levels of protein, and share, and inositol is better[22]. Phytic acid can be selectively inhibit MDA-MB 231 breast cancer cell adhesion, migration of the extracellular matrix effect, can reduce the adhesion of collagen and fibronectin, has no effect on laminin, and extracellular matrix adhesion traction, can provide cell differentiation inducing proliferation signal, cells treated by phytic acid, cell shape more round, no membrane folds, flake pseudopodia, visible migration ability to reduce[23]. 2 mM phytic acid can reduce HT - 29 cell type for I collagen adhesion ability[14]. Phytic acid can also regulate the adhesion between cancer cells and extracellular matrix by regulating the expression of integrin and its receptors.

Integrin, an important cell surface receptor, is a transmembrane heterodimer glycoprotein formed by non-covalently binding of and subunits. It mainly mediates the adhesion between cells and extracellular matrix. Integrins connect the cytoskeleton to the extracellular matrix to form focal adhesions (FAK), which are the basis of integrin signal transduction. Phytic acid can inhibit PI3K signaling pathway, down-regulate the expression of integrin receptors, inhibit the secretion of vesicles, prevent the recovery of integrin, and inhibit cell adhesion. Phytic acid can reduce the expression of α2β1, α5β1 and αvβ3 integrin receptors in human breast cancer cells, reduce focal adhesion, and avoid bone metastasis, possibly by reducing the phosphorylation of adhesion spot kinase[23, 24]. Phytic acid, inositol and the combination of the two can reduce the expression of integrin 1 in mice with liver metastasis from colorectal cancer. When combined, the inhibition effect is stronger[25].

3.4 Phytic acid inhibited the degradation of ECM

by cancer cells and promoted Anoikis

Matrix metalloproteinases (MMPs) play an important role in tumor invasion and metastasis. They can degrade extracellular matrix and basement membrane, destroy physical barriers, and promote tumor cell invasion and metastasis. Tissue inhibitors of matrix metalloproteinases (TIMPs) can regulate the activity of MMPs and inhibit the expression of MMPs. Overexpression of TIMPs will aggravate the invasion and metastasis ability of tumor cells. Phytic acid can regulate the expression of MMPs and TIMPs through MAPK, PKC, PI3K/AKT pathways to inhibit tumor metastasis. Phytic acid can reduce the expression of MMP-9 in human breast cancer cells and colorectal cancer mice[22, 23]. Inositol and the combination of phytic acid and inositol can also reduce the expression of MMP-9 in mice, and the combined effect of the two is better. Phytic acid can also down-regulate the expression of MMP-2, MMP-3, MMP-10, MMP-13 and TIMP-1 and TIMP-2 in Caco-2 cells[26-28].

Phytic acid can inhibit the up-regulation of MMP-2 and MMP-9 by inhibiting the expression of NOS[17]. Phytic acid can also down-regulate MMP-1, MMP-2, MMP-9 and TIMP-2 induced by IL-β[27]. At present, the effect of phytic acid on TIMPs is not clear, and it is worth further study.

When normal cells lack contact with the extracellular matrix or neighboring cells, programmed cell death occurs, which we call "Anoikis." For tumor cells to survive and metastasize, certain mechanisms must be activated to resist Anoikis. Studies have shown that tumor cells can resist Anoikis and autophagy by activating the PI3K/Akt pathway[29]. Phytic acid can promote the apoptosis of HT-29 cells by regulating PI3K/Akt[30].

3.5 Phytic acid can strengthen the intestinal mucosal barrier

Intestinal mucosal barrier plays an important role in preventing the metastasis of tumors. Various substances secreted by intestinal epithelial cells enter the mucus layer, including mucin and TFF family, and play a barrier function. The integrity of the intestinal mucosal barrier limits the movement of tumor cells, making it impossible for them to cross and migrate to other tissues. MUC2 is a major secreted mucin in the colorectal and a major component of the intestinal mucous layer. It forms an elastic gel layer on the intestinal mucosal surface to lubricate and antagonize pathogenic bacteria adhesion and invasion of the intestinal tract. The intervention of phytic acid can improve the expression of MUC2 mRNA and protein levels in colorectal cancer rats, and phytic acid can improve the mechanical barrier of intestinal mucosa by regulating MUC2. TFF family is a small polypeptide molecule synthesized and secreted mainly by epithelial cells of the digestive tract. It has a three-leaf factor domain and plays an important physiological role in mucosal repair. Phytic acid increased the expression of TFF3 mRNA and protein in colorectal tumors. The connection between intestinal epithelial cells plays an important role in maintaining intestinal epithelial integrity.

Tight junctions are one of the most important intercellular junctions, while occludin, zo-1 and claudin-1 are the most important three types of tight junction proteins. zo-1 anchors occludin and Claudin-1 to the cytoskeleton, enhancing tight junctions. In vitro experiments, it was observed that phytic acid could reduce the expression of occludin, zo-1 and claudin-1, and decrease the integrity of tight-junction protein in monolayer of Caco-2 cells, which was antagonized by the addition of calcium and magnesium ions[31]. Phytic acid significantly increased the expression of zo-1 and occludin in colorectal tumors in rats, and down-regulated the expression of claudin-1, indicating that phytic acid can improve the mechanical barrier function of intestinal mucosa by regulating the function of tight junctions in vivo. Phytic acid decreased the level of D-LA in serum and showed a dose-effect relationship, indicating that phytic acid could improve the barrier function of intestinal mucosa during the occurrence of colorectal cancer, and try to avoid d-LA, a macromolecular substance, from entering the blood through the barrier. Phytic acid can reduce the expression of LPS in the blood of colorectal cancer rats, indicating that phytic acid can improve intestinal mucosal injury, protect intestinal mucosal integrity, and effectively inhibit the proliferation of tumor cells to other tissues[32].

3.6 Phytic acid inhibits the migration of tumor cells through blood vessels and lymphatic vessels

Tumor metastasis to spread to other tissues by blood vessels, and the growth of metastases to the formation of new blood vessels, tumor cells can invade the blood vessels and lymphatic vessels, referred to as the circulating tumor cells (CTC), its can endothelial cells adhesion and targets, interaction, and then through the lymphatic vessels, by the proliferation of tumor cells and the formation of blood vessels to form a new nests[32]. Phytic acid can inhibit angiogenic factors, inhibit the formation of new blood vessels, thereby inhibiting tumor metastasis. In patients with rectal cancer metastasis, VEGF protein expression is closely related to clinical stage and tumor invasion and metastasis[33]. VEGF promotes angiogenesis, promotes the extravasation of cancer cells from blood vessels, and is involved in the degradation of extracellular matrix. BFGF can promote the growth of vascular endothelial cells, promote their transformation

into malignant cells, and promote the malignant proliferation of cells. Phytic acid can inhibit the growth of bovine aortic endothelial cells and induce their differentiation[34], and inositol triphosphate can also promote the normalization of blood vessels[35]. In vitro and in vivo experiments have shown that phytic acid and inositol can down-regulate the mRNA and protein expressions of VEGF and bFGF, and reduce the angiogenesis induced by phytic acid and inositol[34].

TGF-β transforming growth factor function complex, can promote the formation of blood vessels. TGF-secreted by platelets also inhibits NK cell activity[36]. TGF-β inhibits tumor development in early cancer, but promotes EMT[37]. Phytic acid can regulate the transformation of growth factors to inhibit tumor metastasis. In a study of a BABL/c mouse model of colorectal cancer liver metastasis, phytic acid, inositol and the combination of the two were found to reduce TGF-β expression. In addition, the combination of the two is better than any single use, and the tumor inhibition rate can be as high as 72.59%[38].

Nitric oxide synthase family (NOS) synthesis of NO plays an important role in blood pressure regulation, relaxation of smooth muscle, neurotransmission, gene transcription and post-translational protein modification, it can also regulate tumor cell migration and angiogenesis. iNOS can regulate VEGF and microvascular density. Phytic acid can inhibit the expression of NOS and achieve anti-metastasis ability[17].

3.7 Phytic acid can enhance the immune ability of the body

The body's immune system plays an important role in suppressing the growth and metastasis of tumors. In the early stages of tumor development, the immune system can effectively inhibit the development of tumor, killing tumor cells, meanwhile, the immune system takes the dominant position. Subsequently, tumor cells evade immune recognition and attack by modifying their own surface antigens and changing the microenvironment around tumor tissues, and secrete a lot of immunosuppressive factors in the form of autocrine, eventually leading to the occurrence of immune escape. Circulating tumor cells (CTC) can express CD47 (a protein that inhibits cytotoxicity and phagocytic activity of activated immune cells), inhibit the role of macrophages and T cells, and induce immune escape through dormancy and camouflage[39]. TGF-β also promotes immune escape from CTC. NK cells prevent the formation of experimental or spontaneous liver metastases and can quickly kill tumor cells that enter the bloodstream. NK cells strongly inhibit tumor metastasis from three aspects: releasing preformed particles containing PRF1 and G2MB, secreting IFNG, and exposing death receptor ligands: FASLG and TRAIL[40]. Arterial injection of adherent NK cells is conducive to the migration of NK cells to the liver, thereby exerting its ability to infiltrate and destroy cancer cells and inhibiting the liver metastasis of tumors[41]. In vivo, NK cells stimulated by IL-2 could inhibit tumor growth and lung metastasis of nude mice with liver cancer, and the number and volume of lung metastasis were significantly reduced compared with those of the untreated NK cell group. In vitro experiments also proved that NK cells could reduce the metastasis and invasion of human liver cancer cells. Phytic acid can enhance NK cell activity in DMH-induced colon cancer mice. In vitro experiments also proved that phytic acid can enhance NK cytotoxicity, and inositol can enhance this effect[42, 43].

3.8 Phytic acid can inhibit the colonization of metastatic tumor

Once circulating tumor cells (CTC) exit the circulation at their metastasis site, they must change their metabolism again to adapt to the new environment of the host organ. Millions of cancer cells flow into the circulatory system through the primary tumor, and only a very small part has the ability to colonize and form metastatic lesions. The most common metastatic site of colorectal cancer is the liver, which accounts for more than 70% of all metastatic organs. The liver microenvironment is suitable for cancer cells that have the characteristics of decomposing high sugar and adapting to low oxygen environment[44].

Shamsuddin A.M. first proved that phytic acid can reduce the growth of subcutaneously transplanted fibrosarcoma in tumor-bearing mice, prolong the life span of mice, and reduce the number of lung metastases[45]. TGF-β can stimulate cancer cells to release osteolytic cytokines to form osteolytic metastases[37]. Phytic acid can inhibit TGF-β, thereby inhibiting tumor colonization. The weight and volume of liver metastases in colorectal cancer mice treated with phytic acid were smaller than those in the non-intervention group, and the effect was better when combined with inositol[22].

4. Conclusion

In conclusion, the metastasis of colorectal cancer is an extremely complex process, which is regulated by many factors, and its molecular mechanism is still unclear. After the occurrence of cancer metastasis, current treatment methods have relatively large side effects and poor prognosis. Therefore, how to find the key nodes in the process of colorectal cancer metastasis, improve the prognosis of patients with

advanced colorectal cancer metastasis, and find safe treatment methods without side effects has become the key. Phytic acid as a safe non-toxic food, its application prospect is very broad, phytic acid can regulate a variety of factors to play its anti-transfer role. Phytic acid can enhance the adhesion between cancer cells, reduce the adhesion between cancer cells and extracellular matrix, limit the movement ability of cancer cells, reduce angiogenesis, regulate MMPs and TIMPs, strengthen the intestinal mucosal barrier, and improve the tumor microenvironment.

Among the numerous studies, there are differences in the results of many studies, some of which are inconsistent with the results of in vitro and in vivo experiments, which need to be further studied.

Of course, there are still many unanswered questions regarding its function and application. Existing data show that its anticancer ability is only moderate[45], and it can only be used for clinical adjuvant therapy and treatment concentration remains high. In the studies on phytic acid, most of them are animal experiments and cell experiments, and there is a lack of large prospective cohort studies and randomized controlled trials, so there are certain ethical problems. There are few studies on the relationship between phytic acid and immune system, which deserve further study.

References

[1] Prynne CJ, Mccarron A, Wadsworth ME, et al. Dietary fibre and phytate--a balancing act: results from three time points in a British birth cohort[J]. Br J Nutr, 2010, 103(2): 274-80.

[2] Forbes RM, Parker HM, Erdman JW, Jr. Effects of dietary phytate, calcium and magnesium levels on zinc bioavailability to rats[J]. J Nutr, 1984, 114(8): 1421-5.

[3] Hunt JR, Johnson PE, Swan PB. Dietary conditions influencing relative zinc availability from foods to the rat and correlations with in vitro measurements[J]. J Nutr, 1987, 117(11): 1913-23.

[4] Rizvi I, Riggs DR, Jackson BJ, et al. Inositol hexaphosphate (IP6) inhibits cellular proliferation in melanoma[J]. J Surg Res, 2006, 133(1): 3-6.

[5] Schlemmer U, Jany KD, Berk A, et al. Degradation of phytate in the gut of pigs--pathway of gastro-intestinal inositol phosphate hydrolysis and enzymes involved[J]. Arch Tierernahr, 2001, 55(4): 255-80.

[6] Schlemmer U, Frølich W, Prieto RM, et al. Phytate in foods and significance for humans: food sources, intake, processing, bioavailability, protective role and analysis[J]. Mol Nutr Food Res, 2009, 53 Suppl 2:S330-75.

[7] Kapral M, Wawszczyk J, Węglarz L. Regulation of MicroRNA-155 and Its Related Genes Expression by Inositol Hexaphosphate in Colon Cancer Cells[J]. Molecules, 2019, 24(22): 4153.

[8] Parfiniewicz B, Pendzich J, Kapral M, et al. The influence of TNF-alpha on concentration of soluble adhesion molecules in cultures of HT-29 cells exposed to inositol hexaphosphate [J]. Acta Pol Pharm, 2012, 69(6): 1291-7.

[9] Cholewa K, Parfiniewicz B, Bednarek I, et al. The influence of phytic acid on TNF-alpha and its receptors genes' expression in colon cancer Caco-2 cells[J]. Acta Pol Pharm, 2008, 65(1): 75-9.

[10] Okazaki Y, Katayama T. Dietary phytic acid modulates characteristics of the colonic luminal environment and reduces serum levels of proinflammatory cytokines in rats fed a high-fat diet [J]. Nutr Res, 2014, 34(12): 1085-91.

[11] Kapral M, Wawszczyk J, Sośnicki S, et al. Down-regulation of inducible nitric oxide synthase expression by inositol hexaphosphate in human colon cancer cells[J]. Acta Pol Pharm, 2015, 72(4): 705-11.

[12] Wawszczyk J, Kapral M, Hollek A, et al. The effect of phytic acid on the expression of NF-kappaB, IL-6 and IL-8 in IL-1beta-stimulated human colonic epithelial cells[J]. Acta Pol Pharm, 2012, 69(6): 1313-9.

[13] Kapral M, Parfiniewicz B, Strzałka-Mrozik B, et al. Evaluation of the expression of transcriptional factor NF-kappaB induced by phytic acid in colon cancer cells[J]. Acta Pol Pharm, 2008, 65(6): 697-702.

[14] Zhang M, Weng W, Zhang Q, et al. The lncRNA NEAT1 activates Wnt/β-catenin signaling and promotes colorectal cancer progression via interacting with DDX5[J]. J Hematol Oncol, 2018, 11(1): 113.

[15] Rubinstein MR, Wang X, Liu W, et al. Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadA adhesin[J]. Cell Host Microbe, 2013, 14(2): 195-206.

[16] Fu M, Song Y, Wen Z, et al. Inositol Hexaphosphate and Inositol Inhibit Colorectal Cancer Metastasis to the Liver in BALB/c Mice[J]. Nutrients, 2016, 8(5): 286.

[17] Tantivejkul K, Vucenik I, Shamsuddin AM. Inositol hexaphosphate (IP6) inhibits key events of cancer metastasis: I. In vitro studies of adhesion, migration and invasion of MDA-MB 231 human breast cancer cells[J]. Anticancer Res, 2003, 23(5a): 3671-9.

[18] Tantivejkul K, Vucenik I, Shamsuddin AM. Inositol hexaphosphate (IP6) inhibits key events of cancer metastasis: II. Effects on integrins and

focal adhesions[J]. Anticancer Res, 2003, 23(5a): 3681-9.
[19] Wang S, Zhang Y, Huang J, et al. TRIM67 Activates p53 to Suppress Colorectal Cancer Initiation and Progression[J]. Cancer Res, 2019, 79(16): 4086-98.
[20] Kapral M, Wawszczyk J, Hollek A, et al. Inhibitory effect of inositol hexaphosphate on metalloproteinases transcription in colon cancer cells stimulated with phorbol-12-myristate 13-acetate[J]. Acta Pol Pharm, 2012, 69(6): 1307-12.
[21] Kapral M, Wawszczyk J, Jurzak M, et al. The effect of inositol hexaphosphate on the expression of selected metalloproteinases and their tissue inhibitors in IL-1β-stimulated colon cancer cells[J]. Int J Colorectal Dis, 2012, 27(11): 1419-28.
[22] Kapral M, Wawszczyk J, Jurzak M, et al. Evaluation of the expression of metalloproteinases 2 and 9 and their tissue inhibitors in colon cancer cells treated with phytic acid[J]. Acta Pol Pharm, 2010, 67(6): 625-9.
[23] Surviladze Z, Sterk RT, Deharo SA, et al. Cellular entry of human papillomavirus type 16 involves activation of the phosphatidylinositol 3-kinase/Akt/mTOR pathway and inhibition of autophagy[J]. J Virol, 2013, 87(5): 2508-17.
[24] Liu G, Song Y, Cui L, et al. Inositol hexaphosphate suppresses growth and induces apoptosis in HT-29 colorectal cancer cells in culture: PI3K/Akt pathway as a potential target[J]. Int J Clin Exp Pathol, 2015, 8(2): 1402-10.
[25] Fu Q, Wang H, Xia M, et al. The effect of phytic acid on tight junctions in the human intestinal Caco-2 cell line and its mechanism[J]. Eur J Pharm Sci, 2015, 80:1-8.
[26] Asc DE-S, Costa-Casagrande TA. ANIMAL MODELS FOR COLORECTAL CANCER[J]. Arq Bras Cir Dig, 2018, 31(2): e1369.
[27] Duan S, Huang W, Liu X, et al. IMPDH2 promotes colorectal cancer progression through activation of the PI3K/AKT/mTOR and PI3K/AKT/FOXO1 signaling pathways[J]. J Exp Clin Cancer Res, 2018, 37(1): 304.
[28] Vucenik I, Passaniti A, Vitolo MI, et al. Anti-angiogenic activity of inositol hexaphosphate (IP6)[J]. Carcinogenesis, 2004, 25(11): 2115-23.
[29] Limani P, Linecker M, Kachaylo E, et al. Antihypoxic Potentiation of Standard Therapy for Experimental Colorectal Liver Metastasis through Myo-Inositol Trispyrophosphate[J]. Clin Cancer Res, 2016, 22(23): 5887-97.
[30] Kopp HG, Placke T, Salih HR. Platelet-derived transforming growth factor-beta down-regulates NKG2D thereby inhibiting natural killer cell antitumor reactivity[J]. Cancer Res, 2009, 69(19): 7775-83.
[31] Massagué J. TGFbeta in Cancer[J]. Cell, 2008, 134(2): 215-30.
[32] Marks G, Aydos RD, Fagundes DJ, et al. Modulation of transforming growth factor beta2 (TGF-beta2) by inositol hexaphosphate in colon carcinogenesis in rats[J]. Acta Cir Bras, 2006, 21 Suppl 4:51-6.
[33] Steinert G, Schölch S, Niemietz T, et al. Immune escape and survival mechanisms in circulating tumor cells of colorectal cancer[J]. Cancer Res, 2014, 74(6): 1694-704.
[34] López-Soto A, Gonzalez S, Smyth MJ, et al. Control of Metastasis by NK Cells[J]. Cancer Cell, 2017, 32(2): 135-54.
[35] Matera L, Galetto A, Bello M, et al. In vivo migration of labeled autologous natural killer cells to liver metastases in patients with colon carcinoma[J]. J Transl Med, 2006, 4:49.
[36] Zhang Z, Song Y, Wang XL. Inositol hexaphosphate-induced enhancement of natural killer cell activity correlates with suppression of colon carcinogenesis in rats[J]. World J Gastroenterol, 2005, 11(32): 5044-6.
[37] Baten A, Ullah A, Tomazic VJ, et al. Inositol-phosphate-induced enhancement of natural killer cell activity correlates with tumor suppression[J]. Carcinogenesis, 1989, 10(9): 1595-8.
[38] Schild T, Low V, Blenis J, et al. Unique Metabolic Adaptations Dictate Distal Organ-Specific Metastatic Colonization[J]. Cancer Cell, 2018, 33(3): 347-54.
[39] Vucenik I, Tomazic VJ, Fabian D, et al. Antitumor activity of phytic acid (inositol hexaphosphate) in murine transplanted and metastatic fibrosarcoma, a pilot study[J]. Cancer Lett, 1992, 65(1): 9-13.