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Editorial

Could We Prevent Colorectal Cancer with Metformin?

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Colorectal cancer (CRC) is the third most worldwide occurring malignancy in humans. There are more than one million new cases annually and it is followed by 700,000 death in 2012 in the world [1]. It is worthy to note that in old (over 75) men and women CRC represents the first and the third site for cancer mortality, correspondingly. Risk of CRC doubling each decade between 40 and 80. Fat and carbohydrates enriched food, boiled and grilled meat, deficit of dietary fibers, smoking, alcoholism, etc. have been shown are factors leading to CRC development [1]. Hyperinsulinemia is one of key factors of pathogenesis of cancer, CRC including [2]. Multistage model of colon carcinogenesis suggests that CRC arise from pre-existing adenomas. A number of genes including APC, p53, and Ki-ras involved into this process. mTOR (mechanistic target of rapamycin) signaling pathway has been recognized as a critical coordinator of cell growth, proliferation and survival [3]. Recently we evaluated results of studies on anticarcinogenic and antitumor effects of antidiabetic biguanides in relation to CRC and perspectives of its wide introduction in clinical practice [4]. Last couple years several new reports on the subject have been published.

In the first time, preventive effect of antidiabetic biguanides on colon carcinogenesis induced with 1,2-dimethylhydrazine (DMH) in rats was demonstrated in 1980 [4]. The treatment with phenformin (PF) decreased by 27.3% a number of colon adenocarcinomas per animal and by 37.5% decreased the average square of colon tumors as compared with rats given DMH only. Treatment with DM H leads to the depletion of dopamine level in the hypothalamus, to decrease of glucose tolerance and an increase of level of serum insulin, cholesterol and triglycerides. The inhibition of lymphocyte blastogenic response to both phytohemagglutinin and lipopolysaccharide as well as a decrease in the rate of production of antibodies against sheep erythrocytes, and a decline in phagocytic activity of macrophages were observed in rats exposed to DMH [4]. These tumor–prone changes in immune response – were significantly alleviated in rats given PF from the first injection of the carcinogen. Preventing effect of metformin (MF) was shown in several models of colon carcinogenesis: MF treatment started before or on the day of the 1st injection of a carcinogen azoxymethane (AOM) or DMH or after the last injection of a carcinogen effectively inhibits colon carcinogenesis in diabetic and non-diabetic rodents (Table 1).

The risk of developing of colon cancer is increased in patients with type 2 diabetes, and may be modified by glucose-lowering therapies. Antidiabetic biguanides were first used as a component of the so-called 'metabolic rehabilitation' regimen of breast and colon cancer patients [2]. The total of 324 patients (182 with breast cancer and 142 with colon cancer) treated by surgery of the primary tumor were randomly divided into control and treatment groups. In the latter group, low saturated fats/low cholesterol diet was combined with treatment with PF or hypolipidemic drugs (mainly clofibrate). Of the patients treated with PF, 304 were treated with the drug for over 3 years and 15% for over 5 years. The authors reported an overall improvement in the cumulative survival by 3 - 6 and 4 - 7 years of observation in groups with breast and colon cancer, respectively, as well as a slight decrease in frequency of primary multiple neoplasms and metachronous tumors in the contralateral breast.

Meta-analysis of 37 studies comprising 1,535,636 participants has shown the risk reduction of colon cancer mortality was reduced by 23% among users of MF as compared with non-users [5]. The majority of epidemiological data and results of clinical trials seems presents sufficient evidence of efficacy of MF in prevention and treatment of CRC in humans [6,7].

Strain	Sex	Carcinogen	Drug	Doses	Route	Effect	References*
Rat							
F344	Male	AOM	MF	15 mg/kg	d.w.	↓	Shimomoto., *et al*. 2012
F344	No data	AOM	MF	500 - 1000 ppm	diet	=	Rao., *et al*. 2011
F344	No data	AOM	MF	1000 ppm	diet	=	Madka., *et al*. 2013
LIO	Female	DMH	PF	5 mg/rat	oral	↓	Anisimov., *et al*. 1980
LIO	Female	DMH	Diabenol	0.1 mg/ml	d.w.	↓	Popovich., *et al*. 2005
SD	Male	DMH	MF	150 mg/kg	oral	↓	Jia., *et al*. 2015
Wistar	Male	DMH	MF	40 - 360 mg/kg	oral	↓	Li., *et al*. 2015
Wistar	Male	DMH	MF	100 - 300 mg/kg	oral	↓	Bekusova., *et al*. 2016
Mouse							
BALB/c	Male and Female	AOM	MF	250 mg/kg	diet	↓	Hosono., *et al*. 2010
BALB/c	M and F	AOM	MF	250 mg/kg	d.w.	↓	Abd., *et al*. 2014
BALB/c	M and F	AOM	MF	250 mg/kg	i.p.	↓	Abd., *et al*. 2014
Swiss albino	Male	DMH	MF	100 - 200 mg/kg	oral	↓	Zaafar., *et al*. 2014
ICR	Male	DMH+DSS	MF	240 mg/kg	oral	↓	Li., *et al*. 2015
BALB/C	Female	DMH	MF	50 mg/kg	d.w.	↓	Bordini., *et al*. 2017

Table 1: *Effect of antidiabetic drugs on chemically-induced colon carcinogenesis in rodents.*

*Notes: *Full references are given in [8].*

Abbreviations: M: Males; F: Females; d.w.: Drinking water; i.p.: Intreperitoneally; ppm: Parts per million. AOM: Azoxymethane; DMH: 1,2-dimethylhydrazine; DSS: Dextran

Epidemiological studies and clinical trials leads us to conclusion that antidiabetic biguanides are impressive samples of successive translation of theoretical considerations into clinical practice. Both *in vitro* and *in vivo* experiments give sufficient evidence of efficacy of biguanides in prevention of spontaneous and induced carcinogenesis [8]. Whereas the majority of clinical observations clearly demonstrates protective effect of MF in relation to many localization of cancer, there are some published results of clinical trials that are inconclusive and sometime were demonstrated adverse effect of MF [6-8].

It is worthy to note that MF has perspectives not only in oncology but also as drug for preventing premature aging (geroprotector). Over the last decade, it was established that conservative growth hormone IGF-1 and mTOR signaling pathways play a key role in the control of aging and age-associated pathology in yeast, worms, insects and mammals [8,9]. Being a key component of mTOR, mTORC1 (mammalian target of rapamycin complex 1) is activated by insulin and related growth factors through phosphatidylinositol-3-OH kinase and AKT kinase signaling, and suppressed by AMP-activated protein kinase, a key sensor of cellular energy status [10,11]. mTORC1 is involved in promoting mRNA translation and protein synthesis through ribosomal protein S6 kinases (S6Ks) and 4E-BP protein. Additionally, mTORC1 stimulates lipid biosynthesis, inhibits autophagy, and finally regulates mitochondrial function and glucose metabolism by the means of HIF-1α(Hypoxia-inducible factor 1-alpha) signaling.

We believe that for taking together all present knowledge, these results allow to suggest MF as a real drug for prevention of colon and some other cancers in populations with type-2 diabetes as well as in non-diabetic persons.

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