Obesity Research & Clinical Practice (2018) xxx, xxx–xxx

REVIEW

# The mechanisms linking obesity to colon cancer: An overview

**Aleksandra Tarasiuk, Paula Mosińska, Jakub Fichna***

*Department of Biochemistry, Faculty of Medicine, Medical University of Lodz, Poland*

Received 28 October 2017; received in revised form 19 January 2018; accepted 26 January 2018

**KEYWORDS**
Obesity;
Colon cancer;
Proinflammatory cytokines;
Adipose tissue

**Summary** Obesity, characterised as a chronic low-grade inflammation is a crucial risk factor for colon cancer. The expansion of the adipose tissue is related to elevated triglyceride and low-density lipoprotein (LDL) levels and hyperinsulinemia, which all are presumed mediators of the tumour development. Obesity is also believed to support carcinogenesis by activating the insulin/IGF-1 pathway. Moreover, obesity increases the level of proinflammatory cytokines (e.g. TNF-α, IL-1, and IL-6) and has a significant impact on selected adipokines.

This paper briefly outlines the latest evidence of the linkage between the obesity and colon cancer and discusses its possible implication for the improvement of anticancer prevention and treatment strategies connected with nutrition.


*Abbreviations:* AP-1, activator protein 1; $AT_1$, type 1 receptors for angiotensin II; ATMs, adipose tissue macrophages; BAT, brown adipose tissue; CLSs, crown-like structures; CRC, colorectal cancer; DGKζ, diacylglycerol kinase ζ; DHA, docosahexaenoic acid; DHEA, docohexaenoylethanolamine; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; GPR120, G protein–coupled receptor 120; HNF-1, hepatocyte nuclear factor 1 alpha; HNF-4α, hepatocyte nuclear factor 4-alpha; IBD, inflammatory bowel disease; IFN-γ, interferon gamma; IGF-1, insulin-like growth factor 1; IL-1, interleukin-1; IL-6, interleukin-6; iNOS, nitric oxide synthase; IR, insulin receptor; IRS1-4, insulin receptor substrate protein; JAK-2, Janus kinase 2; LC-PUFAs, polyunsaturated omega-3 fatty acids; LDL, low-density lipoprotein; LR, leptin receptor; M1, macrophage type I; M2, macrophage type II; MAPK, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein 1; MMR, macrophage mannose receptor 1; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; Ob-Re, soluble form of the leptin receptor; Ob-Rb, Ob-RL, long isoform of the leptin receptor; Ob-Ra, Ob-Rs, short form of the leptin receptor; PAI-1, plasminogen activator inhibitor-1; PGE2, prostaglandin E2; PI3K-Akt, phosphatidylinositol-4,5-bisphosphate 3-kinase; PPAR, peroxisome proliferator-activated receptor; PPARγ, peroxisome proliferator-activated receptor-γ; PRL, prolactin; PRLR, prolactin receptor; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; SAT, subcutaneous adipose tissue; SHP, small heterodimer partner; STAT, signal transducer and activator of transcription; STAT3, signal transducer and activator of transcription 3; Th1, type 1 T helper cell; Th2, type 2 T helper cell; TLR4, toll-like receptor 4; TNF-α, tumour necrosis factor-alpha; UPR, unfolded protein response; VAT, visceral adipose tissue; VEGF, vascular endothelial growth factor; VLDL, very-low-density lipoproteins; WAT, white adipose tissue.

* Corresponding author at: Department of Biochemistry, Faculty of Medicine, Medical University of Lodz, Mazowiecka 6/8, 92-215 Lodz, Poland.

*E-mail address:* jakub.fichna@umed.lodz.pl (J. Fichna).

https://doi.org/10.1016/j.orcp.2018.01.005
1871-403X/

Please cite this article in press as: Tarasiuk A, et al. The mechanisms linking obesity to colon cancer: An overview. Obes Res Clin Pract (2018), https://doi.org/10.1016/j.orcp.2018.01.005

**Contents**



## Introduction

Currently, obesity is described as a global issue and referred to as epidemic; concurrently, colon cancer is the second most common cause of death in developed societies [1,2]. Various factors including gender, ethnic origin, geographical region and environmental conditions (smoking, alcohol, nutrition and dietary habits, sedentary lifestyle and obesity) are associated with colon cancer risk [3,4]. Generally, each type of cancer has at least one common characteristic: uncontrollable cell growth, which can be observed by excessive cell proliferation. However, cancer cells never differentiate — they continue to divide, cause more damage, and invade new tissues which is a result of pro-survival properties [5,6]. Colorectal cancer (CRC) develops as a result of uncontrolled cell growth within the large intestine, including — caecum, the ascending, the transverse, and the descending colon or rectum, hence symptoms and treatment may differ substantially. CRC is more common in men than in women, and rarely occurs before 40 years old; the peak incidence falls on the 7th decade of life [7,8]. The vast majority (90%) of CRCs are carcinomas (adenocarcinomas) of the colon. Individuals with genetic predispositions are at higher risk of earlier CRC development; it can also be triggered by Crohn's disease and ulcerative colitis, as well as smoking. Several factors related to obesity, e.g. proinflammatory cytokines (TNF-α, IL-1, and IL-6), adipokines (leptin, resistin, and adiponectin), chemokines and many more predispose for carcinogenesis, and hence associate with increased risk of CRC [9,10]. Indeed unhealthy diet, too little exercise, contraceptives, alcohol, smoking, and harmful environmental factors can lead to increased body mass index [11,12]. Consequently, these factors are strongly associated with development of CRC. It has been recently reported that patients who were suffering from obesity are more prone to experience higher risk of CRC [13]. Moreover, morbid obesity is not only the main cause of CRC but also it increases mortality and surgical complications after operative period of colorectal cancer [14]. There is no doubt that better understanding of the links between obesity and cancer may be critical for the improvement of CRC prevention and treatment strategies.

## Insulin, hyperinsulinemia and insulin-like growth factor (IGF-1)

Obesity is considered as multifactorial medical condition with a complex phenotype. There are several determinants that are considered as the main underlying factors of obesity, i.e. genetics and the so called lifestyle-dependent aspects — physical inactivity and/or longstanding excessive energy intake [3]. However, not only these fac-

Please cite this article in press as: Tarasiuk A, et al. The mechanisms linking obesity to colon cancer: An overview. Obes Res Clin Pract (2018), https://doi.org/10.1016/j.orcp.2018.01.005