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Linking Obesity to Colorectal Cancer: Recent Insights Into Plausible Biological Mechanisms

Catherine Guffey
University of South Carolina

LINKING OBESITY TO COLORECTAL CANCER: RECENT INSIGHTS INTO PLAUSIBLE BIOLOGICAL MECHANISMS

by

Catherine R. Guffey

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Accepted by:

E. Angela Murphy, Director of Thesis

Daping Fan, Reader

Udai Singh, Reader

Lacy Ford, Vice Provost and Dean of Graduate Studies

DEDICATION

This thesis is dedicated to my parents, Ray and Cathy Guffey, for their infinite support and love. Without them I would not be where I am today and there are no words that could express my gratefulness. It is also dedicated to my sister, Emily Guffey, for being the best sister and friend one could ever hope to have.

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ABSTRACT

Obesity has emerged as a leading environmental risk factor for the development of CRC. However, the mechanisms underlying this relationship have not yet been fully explained. Recent literature has focused on 1) inflammatory processes, 2) adipokines, and 3) estrogen. Obesity-enhanced inflammation is largely orchestrated by increases in adipose tissue macrophages leading to the secretion of TNF-α, MCP-1, and IL-6, all of which are linked to CRC. Adiponectin is decreased with obesity and has been reported to be negatively associated with CRC, while leptin, which is increased, is positively associated with the disease. Estrogen has been shown to influence CRC, although its role remains controversial; some studies have implicated estrogen as being protective, while others have suggested it to be a risk factor. We highlight the most important recent advances that have been made on the aforementioned mechanisms that are thought to link obesity to CRC.

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CHAPTER 1

INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer-related mortality in the United States. Overall survival is highly dependent on disease stage at diagnosis, with the estimated 5-year survival rates range from 85% to 90% for patients with stage I disease to <5% for patients with stage IV disease. The etiology of CRC is complex and involves the interaction of genetic and environmental factors. However, the vast majority of cases can be attributed to environmental causes as they account for >70% of all incidences [30]. Recently, obesity has emerged as a leading environmental risk factor for CRC [29,37,48,49]. In fact, a 5 kg/m^2 increase in body mass index (BMI) has been positively associated with CRC risk[48]. Due to the excessive availability of energy dense food and lack of physical activity, obesity levels have risen dramatically in the United States[42]. Indeed, the prevalence of obesity, defined by a BMI >30 kg/m^2, has now reached 35% with no indication of a decline[42,18]. While there is an abundance of data to support a link between obesity and CRC risk, the mechanisms responsible for this relationship have not yet been fully elucidated and are likely mediated by a complex network of biochemically and immunologically factors produced by adipose tissue. This review will examine the recent literature on the possible mechanisms linking obesity to CRC, with emphasis on the most recent literature and is not intended to be a comprehensive review.

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CHAPTER 2

INFLAMMATION

Inflammation has been linked to every event in the development and progression of CRC including cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis[23,49,6,15]. Furthermore, it is well established that inflammatory bowel diseases, including Crohn's disease and ulcerative coloitis, are linked to an increased risk for the development of CRC. Given that obesity is now considered a low-grade inflammatory condition, a likely pathophysiological mechanism that links obesity to CRC risk is chronic inflammation.

2.1 MACROPHAGES

Obesity-induced inflammation is largely mediated through quantitative and functional alterations in white adipose tissue macrophages[56,36,20]. It has been reported that approximately 45-60% of adipose tissue cells express the macrophage marker EMR1 (F4/80) in obese mice, whereas only 10-15% of adipose tissue cells from lean mice express this marker[56]. In addition, adipose tissue macrophages exhibit a pro-inflammatory, classical phenotype (M1) in obese mice, while those from lean mice have an alternatively-activated, anti-inflammatory phenotype (M2)[36]. We recently reported that a high fat diet, closely mimicking the macronutrient content of the American standard diet, can lead to increased obesity that is associated with pro-inflammatory macrophage behavior[14]. Given the propensity for adipose tissue macrophages to assume an inflammatory phenotype and the well-characterized link between inflammation and CRC, it is likely that macrophages play a necessary role in the link between obesity and CRC. However, no studies have used manipulation techniques to directly determine the

role of adipose tissue macrophages in the progression of this disease. Nonetheless, the current evidence for a necessary role of macrophage-induced inflammatory mediators, which are known to activate pathways that can promote CRC, is relatively strong.

2.2 TUMOR NECROSIS FACTOR-ALPHA

Following excessive lipid accumulation, tumor necrosis factor alpha (TNF-α) is produced by adipose tissue macrophages and also to a lesser degree by adipocytes and preadipocytes. Although elevated TNF-α has been widely documented in adipose tissue with obesity, data on obesity-associated TNF-α in the colon is just now beginning to appear in the literature. Liu et al., reported a >70% increase in expression and concentration of TNF-α in the colon following 17 weeks of high fat diet feedings, which was associated with an increase in β-catenin, the key effector of Wnt signaling[35]. In addition, an elegant study by Flores et al., examined the role of TNF-α on obesity-induced CRC in mice[19]. They reported that high fat diet feeding increased TNF-α expression in the colon that was associated with a larger number of tumors, increased proliferation, and decreased apoptosis[19]. When TNF-α was inhibited, these effects were reversed; inhibition of TNF-α restored tumor number and the apoptosis/proliferation profile to levels observed in a lean mouse[19]. A recent clinical study examined TNF-α, among other cytokines, in rectosigmoid mucosal biopsies of 10 obese premenopausal women before and after weight loss[47]. Weight loss (10%) was associated with a significant decrease in TNF-α concentration indicating a reduction in colorectal inflammation[47]. However, another study reported no change in circulating levels of TNF-α in obese patients or CRC patients compared to controls[26]. Similarly, there was no relationship reported between BMI and circulating TNF-α and risk for CRC in colorectal

adenoma patients[28]. Although the clinical evidence is relatively limited, the recent controlled experimental studies in rodents support a role of TNF-α in obesity-enhanced CRC.

2.3 MONOCYTE CHEMOATTRACTANT PROTEIN-1

Monocyte chemoattractant protein 1 (MCP-1) has been identified as an essential chemokine for monocyte trafficking. It has been reported to contribute to tissue macrophage accumulation by inducing a chronic inflammatory state. A recent investigation transferred wild-type monocytes to MCP-1$^{-/-}$ recipients and reported that adipose tissue macrophage accumulation was reduced by ~40%, implicating the MCP-1 system as a major contributory factor to monocyte migration into adipose tissue[43]. Incidentally, it has also been implicated as an important chemokine for macrophage recruitment in several human tumors including CRC and has been associated with increased grade of the tumor as well as poor prognosis[45,58]. McClellan et al. recently reported an increase in MCP-1 in intestinal tissue in a mouse model of CRC that was positively correlated with the percentage of large polyps[38]. Subsequently, they crossed the *Apc*$^{Min/+}$ mouse model of intestinal tumorigenesis with an MCP-1$^{-/-}$ mouse to examine the role of this chemokine in CRC[39]. MCP-1 deficiency decreased overall polyp number as well as large polyp number[39]. Further, macrophage positive cells were decreased in the polyp tissue as well as expression of markers associated with M1& M2 macrophages as well as T regulatory cells , while markers for cytotoxic T cells were increased[39]. In addition, MCP-1$^{-/-}$ offset the increased expression of inflammatory mediators in polyp tissue[39]. Similarly, Bailey et al. has reported that MCP-1 expression is associated with tumor associated macrophage number and stage of CRC in humans[7] and recently,

Hilenbrand et al., reported that circulating MCP-1 was increased in both obese patients and CRC patients[26]. Conversely, a recent report showed lower MCP-1 levels in CRC patients compared to controls[30]. Although there have been no studies that have specifically examined the role of MCP-1 in obesity-enhanced CRC, the evidence in the independent models largely support a disease-promoting effect of MCP-1 in both obesity and CRC.

2.4 IINTERLEUKIN-6

Interleukin (IL)-6, an inflammatory cytokine released by adipocytes and adipose tissue macrophages during obesity[11], may play a role in obesity-enhanced CRC[21]. In fact, epidemiological studies indicate an association between IL-6 and CRC and controlled experiments in mice substantiate these claims[55,24]. For example, Baltgalvis et al., reported that IL-6 deficiency reduced the number of large polyps by approximately 30% in the *Apc*$^{Min/+}$ mouse, the effects of which were reversed when IL-6 was overexpressed[8]. A recent clinical study reported that IL-6 expression is a prognostic marker of tumor behavior in stage III CRC patients[32]. Similarly, high levels of circulating IL-6 have been found to be associated with advanced CRCs[30]. Furthermore, in individuals with adenoma, levels of IL-6 were positively correlated with BMI, insulin and insulin resistance[52]. The mechanisms for IL-6-induced tumorigenesis are thought to be mediated, at least in part, via activation of signal transducers and activators of transcription 3 (STAT3). A recent report documented increased IL6 and p-STAT3-positive epithelial cells in patients with active ulcerative colitis compared to patients with inactive ulcerative colitis or controls[33] and in dysplasia and CRC, significantly more epithelial cells expressed IL6 and p-STAT3 compared with controls[33]. To our

knowledge there are no studies that have specifically examined the role of IL-6 on CRC in an obesity setting. However, it is clear that IL-6, which is increased with obesity, can influence CRC.

CHAPTER 3

ADIPOKINES

In addition to their traditional role in energy homeostasis, adipose-derived hormones (adipokines) have been implicated as potential mediators of the effects of obesity on CRC risk. Adiponectin and leptin, two of the most abundant adipokines, are altered during adipose tissue dysfunction (i.e. obesity) and have been strongly associated with the pathogenesis of CRC.

3.1 ADIPONECTIN

Adiponectin, an adipokine secreted exclusively by adipose tissue, is decreased in obese subjects, likely increasing their propensity for the development of CRC. Several recent mechanistic studies using mice have made substantial advancements in our understanding of the role of adiponectin in CRC. For example, Saxena et al. examined the effect of adiponectin deficiency on chronic inflammation-induced CRC[53]. They reported that deficiency of adiponectin results in more severe symptoms along with a greater number and larger area of tumors that included higher immune cell infiltration and inflammation compared to wild-type mice[53]. Adiponectin knockout mice also showed higher secretion of the pro-inflammatory cytokines including IL-6, IL-1β, and TNF-α and a reduction in the anti-inflammatory cytokine IL-10[53]. The concluded that APN deficiency plays an important role in contributing to inflammation-induced colon cancer due to the increased severity of symptoms, the up-regulation of pro-cancerous and

downregulation of anti-cancerous and inflammatory genes, and the absence of APN-induced downregulation of secretion of pro-inflammatory cytokines. Similarly, a recent study by Moon et al. precisely examined the role of adiponectin on CRC in the settings of obesity[40]. They found that mice fed a high fat diet had larger tumors than those fed a low fat diet but adiponectin administration reversed this effect[40]. Adiponectin treatment also suppressed angiogenesis in tumors as indicated by fewer dense microvessel areas and a reduction in mRNA expression of VEGF[40]. While IL-12, a cytokine that has been associated with anti-tumor properties was increased following adiponectin treatment, in contrast to the findings of Saxena et al., serum cytokine (IFN-γ, IL-2, IL-4, IL-5, IL-10 and TNF-α) levels were unchanged[40]. To further address the mechanisms for this effect they completed a series of *in vitro* studies and found that adiponectin directly controls malignant potential (cell proliferation, adhesion, invasion and colony formation) and regulates metabolic (AMPK/S6), inflammatory (STAT3/VEGF) and cell cycle (p21/p27/p53/cyclins) signaling pathways in both mouse and human colon cancer cells lines[40]. These results highlight the importance of adiponectin in the growth and development of CRC, inflammatory processes, and suggest that the adiponectin deficiency that is a characteristic of obesity plays an important role in the biochemistry of CRC.

Consistent with the animal literature, clinical studies also support a potential role for adiponectin in the link between obesity and CRC. A recent study reported a decrease in serum adiponectin levels in CRC patients compared to controls as well as a negative correlation between adiponectin levels and stage of disease[22]. In contrast to Hillenbrand et al., which reported a decrease in adiponectin in obese patients, the levels reported for

CRC patients were not different from the control samples[26]. These conflicting findings may be result from the lack of differentiation of adiponectin fractions in these studies; adiponectin fractions are hypothesized to have different biological activities (i.e. high molecular weight (HMW) adiponectin is thought to regulate insulin sensitivity whereas non-HMW adiponectin plays a role in the inflammatory response). In support of this hypothesis, Aleksandrova et al. reported that total adiponectin and non-HMW adiponectin concentrations were inversely associated with risk of CRC but there was no association for HMW adiponectin[3]. While the animal studies support a role of adiponectin in CRC, investigation of the relative importance of different adiponectin fractions in CRC pathogenesis is necessary prior to the development of effective clinical therapeutic strategies.

3.2 LEPTIN

Most studies have found that leptin levels increase in direct proportion to body fat and thus are elevated in obese individuals. The results from research on the effect of leptin on CRC risk are contradictory. While there is an abundance of literature to implicate leptin as a potential mediator between obesity and CRC, the exact mechanisms have not yet been elucidated, which is not surprising given the inconsistencies in the literature. In some studies, elevated serum leptin levels were associated with a more positive clinical outcome[46], including overexpression of the long-form signaling receptor, ObRb, which may allow leptin to activate inflammatory genes[4,54] and stimulate inflammatory responses in tumour colonocytes, leading to recruitment of cytotoxic T-cells within the tumor microenvironment[1]. In other studies, decreased serum leptin levels were found in CRC patients[9]. Nonetheless, recent studies have advanced our

understanding of the role of this adipokine in CRC. The proposed link between leptin and CRC was driven initially by reports of leptin receptor expression by various human epithelial colon cancer cell lines. When bound to leptin, the receptor can activate signal transduction pathways that are thought to enhance cell proliferation and DNA synthesis. For example, Fenton et al., reported that leptin promotes the proliferation of preneoplastic (IMCE) cells[17]. While the *in vitro* evidence is relatively strong, there are mixed reports among the animal studies. For instance, an earlier study reported that leptin failed to promote growth of colon cancer xenografts in nude mice and did not increase intestinal tumorigenesis in $Apc^{Min/+}$ mice[5]. In contrast, a more recent study found a significant decrease of tumor cell proliferation in leptin-deficient tumors, as well as a dramatic inhibition of tumor growth in leptin-deficient and leptin-receptor-deficient mice despite the animals exhibiting severe obesity[13]. This ability of leptin to regulate CRC growth was mediated by colonic leptin signaling via the leptin receptor/signal transducer and activator of transcription 3 (STAT3) pathway, suggesting that leptin signaling is a direct pathway that is critical for CRC growth and not merely a bystander of the established relationship between obesity and CRC[13].

Although clinical investigations have provided evidence for a link between leptin and CRC, like the animal studies, there are some inconsistencies among findings. A recent study by Aleksandrova et al. examined the association of leptin and soluble leptin receptor, which has been found to regulate leptin's physiologic functions, with the risk of CRC in a prospective nested case-control study[2]. They reported that soluble leptin receptor was strongly and inversely associated with CRC risk but there was no association found for leptin and CRC risk[2]. And in fact, another study reported that

leptin concentrations were actually decreased in CRC patients[26]. In contrast, in a case-cohort study design, it was found that leptin has an independent effect on CRC in post-menopausal women[27]. Based on the recent literature it is likely that leptin plays a significant role in CRC; however, additional studies are needed to confirm this relationship and to clarify the exact mechanisms underlying these effects.

3.3 ESTROGEN

Estrogen is increased with obesity and has been shown to influence CRC, although its role remains controversial. While some studies have implicated estrogen as being protective in CRC, others have suggested it to be an independent risk factor. Recent evidence favors a protective effect of estrogen receptor-β (Erβ). For example, a greater number of tumors and an increased inflammatory response were documented in Erβ deficient mice[51]. Also, Erβ expression has also been shown to increase apoptosis, downregulate IL-6, increase repair of DNA damage, and change gene transcription[12]. ERα has been associated with an increase colon cancer cell proliferation and increase cancer incidence. For example, it was reported that ovariectomy protects female mice against colitis associated CRC, while estrogen replacement promotes inflammation and tumor development[25]. Chen and Iverson hypothesize that the variation in results among these previous studies may be due to estrogen acting through two different estrogen receptors (ERα and ERβ)[10]. Further, the pro-tumorigenic effects were found to be dependent on both Erα and Erβ[25]. The clinical literature largely supports a protective effect of estrogen; a recent study reported that lack of Erβ expression in tumors was associated with higher cancer stages as well as greater tumor extent[50]. Further, Erβ negativity was associated with an increased hazard ratio for death, death attributed to

CRC, as well as a poorer disease-free survival. Consistently, Fang et al. reported that low expression of tumor Erβ is a risk factor for overall survival in patients with stage II colon cancer[16] and postmenopausal hormone therapy is associated with reduced risk of CRC[54]. An interesting finding from a study by Yi KW et al. showed that ERα agonist increased adipocyte production of leptin while ERα antagonist decreased leptin production[57]. The effect of ERβ agonists was the opposite in that they lead to decreased leptin production, while ERβ antagonists increase leptin production[57]. In contrast, ERs were not associated with changes of other adipokines examined in this study, including adiponectin[57]. These findings are consistent with a recent study, which showed that Erβ agonist silibinin decreased leptin[41]. The effect that obesity has on this relationship remains elusive due to its different actions through two different receptor subtypes. In general, the current evidence supports a protective effect of estrogen, and specifically Erβ, in CRC. However, the exact mechanisms have not yet been determined.

CHAPTER 4

CONCLUSION

The development of the majority of CRCs is largely influenced by non-genetic factors such as obesity. Therefore, a large body of research is now focused on understanding the molecular links between obesity and CRC. While inflammatory mediators, adipokines, and estrogen have all been implicated as causative agents, there have been some inconsistencies in the literature and there is a shortage of evidence in the setting of obesity. Future studies should explore these mechanisms specifically in obesity models. And further, should examine interactions between these factors as it is likely that this relationship is mediated by a complex network of interrelated mechanisms.

REFERENCES

1. Ablohassani M, Aloulou N, Chaumett MT, et al. Leptin receptor-related immune response in colorectal cancers: the role of colonocytes and interleukin-8. Cancer res 2008;68:9423-9432.

2. Aleksandrova K, Boeing H, Jenab M, et al. Leptin and soluble leptin receptor in risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition cohort. Cancer Res 2012;72:5328-37.

3. Aleksandrova K, Boeing H, Jenab M, et al. Total and high-molecular weight adiponectin and risk of colorectal cancer: the European Prospective Investigation into Cancer and Nutrition Study. Carcinogenesis 2012;33:1211-8.

4. Aloulou N, Bastuji-Garin S, Le Gouvello S, et al. Involvement of the leptin receptor in the immune response in intestinal cancer. Cancer Res 2008;68(22):9413-22.

5. Aparicio T, Kotelevets L, Tsocas A, et al. Leptin stimulates the proliferation of human colon cancer cells in vitro but does not promote the growth of colon cancer xenografts in nude mice or intestinal tumorigenesis in Apc(Min/+) mice. Gut 2005;54:1136-45.

6. Balkwill FR, Mantovani A. Cancer-related inflammation: common themes and therapeutic opportunities. Semin Cancer Biol 2012;22:33-40.

7. Bailey C, Negus R, Morris A, et al. Chemokine expression is associated with the accumulation of tumour associated macrophages (TAMs) and progression in human colorectal cancer. Clin Exp Metastasis 2007;24:121-30.

8. Baltgalvis KA, Berger FG, Pena MM, Davis JM, Muga SJ, Carson JA. Interleukin-6 and cachexia in ApcMin/+ mice. Am J Physiol Regul Integr Comp Physiol 2008;294:R393-401.

9. Bolukbas FF, Kilic H, Bolukbas C, et al. Serum leptin concentration and advanced gastronintestinal cancers: a case controlled study. BMC Cancer 2004;4(29).

10. Chen J, Iverson D. Estrogen in obesity-associated colon cancer: friend or foe? Protecting postmenopausal women but promoting late-stage colon cancer. Cancer Causes Control. 2012;23(11):1767-73.

11. Eder K, Baffy N, Falus A, Fulop AK. The major inflammatory mediator interleukin-6 and obesity. Inflamm Res 2009;58:727-36.

12. Edvardsson K, Boeing H, Jenab M, et al. Estrogen receptor beta expression induces changes in the microRNA pool in human colon cancer cells. Carcinogenesis 2011; [Epup ahead of print].

13. Endo H, Hosono K, Uchiyama T, et al. Leptin acts as a growth factor for colorectal tumours at stages subsequent to tumour initiation in murine colon carcinogenesis. Gut 2011;60:1363-71.

14. Enos RT, Davis JM, Velazquez KT, et al. Influence of dietary saturated fat content on adiposity, macrophage behavior, inflammation, and metabolism: composition matters. J Lipid Res 2013;54:152-63.

15. Erreni M, Mantovani A, Allavena P. Tumor-associated Macrophages (TAM) and Inflammation in Colorectal Cancer. Cancer Microenviron 2011;4:141-54.

16. Fang YJ, Zhang L, Wu XJ, et al. Impact of ERbeta and CD44 expression on the prognosis of patients with stage II colon cancer. Tumour Biol 2012;33:1907-14.

17. Fenton JI, Hursting SD, Perkins SN, Hord NG. Leptin induces an Apc genotype-associated colon epithelial cell chemokine production pattern associated with macrophage chemotaxis and activation. Carcinogenesis 2007;28:455-64.

18. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA 2012;307:491-7.

19. Flores MB, Rocha GZ, Damas-Souza DM, et al. Obesity-Induced Increase in Tumor Necrosis Factor-alpha Leads to Development of Colon Cancer in Mice. Gastroenterology 2012;143:741-53 e4.

20. Fujisaka S, Usui I, Bukhari A, et al. Regulatory mechanisms for adipose tissue M1 and M2 macrophages in diet-induced obese mice. Diabetes 2009;58:2574-82.

21. Ghosh S, Ashcraft K. An IL-6 link between obesity and cancer. Front Biosci (Elite Ed) 2013;5:461-78.

22. Gonullu G, Kahraman H, Bedir A, Bektas A, Yucel I. Association between adiponectin, resistin, insulin resistance, and colorectal tumors. Int J Colorectal Dis 2010;25:205-12.

23. Grizzi F, Bianchi P, Malesci A, Laghi L. Prognostic value of innate and adaptive immunity in colorectal cancer. World J Gastroenterol 2013;19:174-84.

24. Guthrie GJ, Roxburgh CS, Horgan PG, McMillan DC. Does interleukin-6 link explain the link between tumour necrosis, local and systemic inflammatory responses and outcome in patients with colorectal cancer? Cancer Treat Rev 2013;39:89-96.

25. Heijmans J, Wielenga MC, Rosekrans SL, et al. Oestrogens promote tumorigenesis in a mouse model for colitis-associated cancer. Gut 2013. doi:10.1136/gutjnl-2012-304216.

26. Hillenbrand A, Fassler J, Huber N, et al. Changed adipocytokine concentrations in colorectal tumor patients and morbidly obese patients compared to healthy controls. BMC Cancer 2012;12:545.

27. Ho GY, Wang T, Gunter MJ, et al. Adipokines linking obesity with colorectal cancer risk in postmenopausal women. Cancer Res 2012;72:3029-37.

28. Hopkins MH, Flanders WD, Bostick RM. Associations of circulating inflammatory biomarkers with risk factors for colorectal cancer in colorectal adenoma patients. Biomark Insights 2012;7:143-50.

29. Jafri SH, Mills G. Lifestyle modification in colorectal cancer patients: an integrative oncology approach. Future Oncol 2013;9:207-18.

30. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-49.

31. Kantola T, Klintrup K, Vayrynen JP, et al. Stage-dependent alterations of the serum cytokine pattern in colorectal carcinoma. Br J Cancer 2012;107:1729-36.

32. Lee WS, Baek JH, You DH, Nam MJ. Prognostic value of circulating cytokines for stage III colon cancer. J Surg Res. 2012; http://dx.doi.org/10.1016/j.jss.2012.08.051.

33. Li Y, de Haar C, Chen M, et al. Disease-related expression of the IL6/STAT3/SOCS3 signalling pathway in ulcerative colitis and ulcerative colitis-related carcinogenesis. Gut 2010;59:227-35.

34. Lin JH, Morikawa T, Chan AT, et al. Postmenopausal hormone therapy is associated with a reduced risk of colorectal cancer lacking CDKN1A expression. Cancer Res 2012;72:3020-8.

35. Liu Z, Brooks RS, Ciappio ED, et al. Diet-induced obesity elevates colonic TNF-alpha in mice and is accompanied by an activation of Wnt signaling: a mechanism for obesity-associated colorectal cancer. J Nutr Biochem 2012;23:1207-13.

36. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007;117:175-84.

37. Ma Y, Yang Y, Wang F, et al. Obesity and risk of colorectal cancer: a systematic review of prospective studies. PLoS One 2013;8:e53916.

38. McClellan JL, Davis JM, Steiner JL, et al. Intestinal inflammatory cytokine response in relation to tumorigenesis in the Apc(Min/+) mouse. Cytokine 2012;57:113-9.

39. McClellan JL, Davis JM, Steiner JL, et al. Linking tumor associated macrophages, inflammation, and intestinal tumorigenesis: Role of MCP-1. Am J Physiol Gastrointest Liver Physiol.2012; 303(10):G1087-95.

40. Moon HS, Liu X, Nagel JM, et al. Salutary effects of adiponectin on colon cancer: in vivo and in vitro studies in mice. Gut 2013; 62(4):561-70.

41. Nejati-Koshki K, Zarghami N, Pourhassan-Moghaddam M, et al. Inhibition of leptin gene expression and secretion by silibinin: possible role of estrogen receptors. Cytotechnology 2012;64(6):719-26.

42. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. JAMA 2012;307:483-90.

43. Oh DY, Morinaga H, Talukdar S, Bae EJ, Olefsky JM. Increased macrophage migration into adipose tissue in obese mice. Diabetes 2012;61:346-54.

44. Okayama H, Schetter AJ, Harris CC. MicroRNAs and inflammation in the pathogenesis and progression of colon cancer. Dig Dis 2012;30 Suppl 2:9-15.

45. Ono M. Molecular links between tumor angiogenesis and inflammation: inflammatory stimuli of macrophages and cancer cells as targets for therapeutic strategy. Cancer Sci 2008;99:1501-6.

46. Paik SS, Jang SM, Jang KS, et al. Letpin expression correlates with favorable clinicopathologic phenotype and better prognosis in colorectal adenocarcinoma. Ann Surg Oncol 2009;16:297-303.

47. Pendyala S, Neff LM, Suarez-Farinas M, Holt PR. Diet-induced weight loss reduces colorectal inflammation: implications for colorectal carcinogenesis. Am J Clin Nutr 2011;93:234-42.

48. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371:569-78.

49. Rickles AS, Iannuzzi JC, Mironov O, et al. Visceral obesity and colorectal cancer: are we missing the boat with BMI? J Gastrointest Surg 2013;17:133-43; discussion p 43.

50. Rudolph A, Toth C, Hoffmeister M, et al. Expression of oestrogen receptor beta and prognosis of colorectal cancer. Br J Cancer 2012;107:831-9.

51. Saleiro D, Murillo G, Benya RV, Bissonnette M, Hart J, Mehta RG. Estrogen receptor-beta protects against colitis-associated neoplasia in mice. Int J Cancer 2012;131:2553-61.

52. Sasaki Y, Takeda H, Sato T, et al. Serum Interleukin-6, insulin, and HOMA-IR in male individuals with colorectal adenoma. Clin Cancer Res 2012;18:392-9.

53. Saxena A, Chumanevich A, Fletcher E, et al. Adiponectin deficiency: role in chronic inflammation induced colon cancer. Biochim Biophys Acta 2012;1822:527-36.

54. Uddin S, Bavi PP, Hussain AR, et al. Leptin receptor expression in Middle Eastern colorectal cancer and its potential clinical implication. Carcinogenesis 2009;30(11):1832-40.

55. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003;112:1796-808.

56. Waldner MJ, Foersch S, Neurath MF. Interleukin-6--a key regulator of colorectal cancer development. Int J Biol Sci 2012;8:1248-53.

57. Yi KW, Shin JH, Seo HS, et al. Role of estrogen receptor-alpha in regulating leptin expression in 3T2-L1 adipocytes. Obesity (Silver Spring) 2008;16(11):2393-2399.

58. Yoshidome H, Kohno H, Shida T, et al. Significance of monocyte chemoattractant protein-1 in angiogenesis and survival in colorectal liver metastases. Int J Oncol 2009;34:923-30.

BIBLIOGRAPHY

Ablohassani M, Aloulou N, Chaumett MT, et al. Leptin receptor-related immune response in colorectal cancers: the role of colonocytes and interleukin-8. Cancer res 2008;68:9423-9432.

Aleksandrova K, Boeing H, Jenab M, et al. Leptin and soluble leptin receptor in risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition cohort. Cancer Res 2012;72:5328-37.

Aleksandrova K, Boeing H, Jenab M, et al. Total and high-molecular weight adiponectin and risk of colorectal cancer: the European Prospective Investigation into Cancer and Nutrition Study. Carcinogenesis 2012;33:1211-8.

Aloulou N, Bastuji-Garin S, Le Gouvello S, et al. Involvement of the leptin receptor in the immune response in intestinal cancer. Cancer Res 2008;68(22):9413-22.

Aparicio T, Kotelevets L, Tsocas A, et al. Leptin stimulates the proliferation of human colon cancer cells in vitro but does not promote the growth of colon cancer xenografts in nude mice or intestinal tumorigenesis in Apc(Min/+) mice. Gut 2005;54:1136-45.

Balkwill FR, Mantovani A. Cancer-related inflammation: common themes and therapeutic opportunities. Semin Cancer Biol 2012;22:33-40.

Bailey C, Negus R, Morris A, et al. Chemokine expression is associated with the accumulation of tumour associated macrophages (TAMs) and progression in human colorectal cancer. Clin Exp Metastasis 2007;24:121-30.

Baltgalvis KA, Berger FG, Pena MM, Davis JM, Muga SJ, Carson JA. Interleukin-6 and cachexia in ApcMin/+ mice. Am J Physiol Regul Integr Comp Physiol 2008;294:R393-401.

Bolukbas FF, Kilic H, Bolukbas C, et al. Serum leptin concentration and advanced gastronintestinal cancers: a case controlled study. BMC Cancer 2004;4(29).

Chen J, Iverson D. Estrogen in obesity-associated colon cancer: friend or foe? Protecting postmenopausal women but promoting late-stage colon cancer. Cancer Causes Control. 2012;23(11):1767-73.

Eder K, Baffy N, Falus A, Fulop AK. The major inflammatory mediator interleukin-6 and obesity. Inflamm Res 2009;58:727-36.

Edvardsson K, Boeing H, Jenab M, et al. Estrogen receptor beta expression induces changes in the microRNA pool in human colon cancer cells. Carcinogenesis 2011; [Epup ahead of print].

Endo H, Hosono K, Uchiyama T, et al. Leptin acts as a growth factor for colorectal tumours at stages subsequent to tumour initiation in murine colon carcinogenesis. Gut 2011;60:1363-71.

Enos RT, Davis JM, Velazquez KT, et al. Influence of dietary saturated fat content on adiposity, macrophage behavior, inflammation, and metabolism: composition matters. J Lipid Res 2013;54:152-63.

Erreni M, Mantovani A, Allavena P. Tumor-associated Macrophages (TAM) and Inflammation in Colorectal Cancer. Cancer Microenviron 2011;4:141-54.

Fang YJ, Zhang L, Wu XJ, et al. Impact of ERbeta and CD44 expression on the prognosis of patients with stage II colon cancer. Tumour Biol 2012;33:1907-14.

Fenton JI, Hursting SD, Perkins SN, Hord NG. Leptin induces an Apc genotype-associated colon epithelial cell chemokine production pattern associated with macrophage chemotaxis and activation. Carcinogenesis 2007;28:455-64.

Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA 2012;307:491-7.

Flores MB, Rocha GZ, Damas-Souza DM, et al. Obesity-Induced Increase in Tumor Necrosis Factor-alpha Leads to Development of Colon Cancer in Mice. Gastroenterology 2012;143:741-53 e4.

Fujisaka S, Usui I, Bukhari A, et al. Regulatory mechanisms for adipose tissue M1 and M2 macrophages in diet-induced obese mice. Diabetes 2009;58:2574-82.

Ghosh S, Ashcraft K. An IL-6 link between obesity and cancer. Front Biosci (Elite Ed) 2013;5:461-78.

Gonullu G, Kahraman H, Bedir A, Bektas A, Yucel I. Association between adiponectin, resistin, insulin resistance, and colorectal tumors. Int J Colorectal Dis 2010;25:205-12.

Grizzi F, Bianchi P, Malesci A, Laghi L. Prognostic value of innate and adaptive immunity in colorectal cancer. World J Gastroenterol 2013;19:174-84.

Guthrie GJ, Roxburgh CS, Horgan PG, McMillan DC. Does interleukin-6 link explain the link between tumour necrosis, local and systemic inflammatory responses and outcome in patients with colorectal cancer? Cancer Treat Rev 2013;39:89-96.

Heijmans J, Wielenga MC, Rosekrans SL, et al. Oestrogens promote tumorigenesis in a mouse model for colitis-associated cancer. Gut 2013. doi:10.1136/gutjnl-2012-304216.

Hillenbrand A, Fassler J, Huber N, et al. Changed adipocytokine concentrations in colorectal tumor patients and morbidly obese patients compared to healthy controls. BMC Cancer 2012;12:545.

Ho GY, Wang T, Gunter MJ, et al. Adipokines linking obesity with colorectal cancer risk in postmenopausal women. Cancer Res 2012;72:3029-37.

Hopkins MH, Flanders WD, Bostick RM. Associations of circulating inflammatory biomarkers with risk factors for colorectal cancer in colorectal adenoma patients. Biomark Insights 2012;7:143-50.

Jafri SH, Mills G. Lifestyle modification in colorectal cancer patients: an integrative oncology approach. Future Oncol 2013;9:207-18.

Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-49.

Kantola T, Klintrup K, Vayrynen JP, et al. Stage-dependent alterations of the serum cytokine pattern in colorectal carcinoma. Br J Cancer 2012;107:1729-36.

Lee WS, Baek JH, You DH, Nam MJ. Prognostic value of circulating cytokines for stage III colon cancer. J Surg Res. 2012; http://dx.doi.org/10.1016/j.jss.2012.08.051.

Li Y, de Haar C, Chen M, et al. Disease-related expression of the IL6/STAT3/SOCS3 signalling pathway in ulcerative colitis and ulcerative colitis-related carcinogenesis. Gut 2010;59:227-35.

Lin JH, Morikawa T, Chan AT, et al. Postmenopausal hormone therapy is associated with a reduced risk of colorectal cancer lacking CDKN1A expression. Cancer Res 2012;72:3020-8.

Liu Z, Brooks RS, Ciappio ED, et al. Diet-induced obesity elevates colonic TNF-alpha in mice and is accompanied by an activation of Wnt signaling: a mechanism for obesity-associated colorectal cancer. J Nutr Biochem 2012;23:1207-13.

Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007;117:175-84.

Ma Y, Yang Y, Wang F, et al. Obesity and risk of colorectal cancer: a systematic review of prospective studies. PLoS One 2013;8:e53916.

McClellan JL, Davis JM, Steiner JL, et al. Intestinal inflammatory cytokine response in relation to tumorigenesis in the Apc(Min/+) mouse. Cytokine 2012;57:113-9.

McClellan JL, Davis JM, Steiner JL, et al. Linking tumor associated macrophages, inflammation, and intestinal tumorigenesis: Role of MCP-1. Am J Physiol Gastrointest Liver Physiol.2012; 303(10):G1087-95.

Moon HS, Liu X, Nagel JM, et al. Salutary effects of adiponectin on colon cancer: in vivo and in vitro studies in mice. Gut 2013; 62(4):561-70.

Nejati-Koshki K, Zarghami N, Pourhassan-Moghaddam M, et al. Inhibition of leptin gene expression and secretion by silibinin: possible role of estrogen receptors. Cytotechnology 2012;64(6):719-26.

Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. JAMA 2012;307:483-90.

Oh DY, Morinaga H, Talukdar S, Bae EJ, Olefsky JM. Increased macrophage migration into adipose tissue in obese mice. Diabetes 2012;61:346-54.

Okayama H, Schetter AJ, Harris CC. MicroRNAs and inflammation in the pathogenesis and progression of colon cancer. Dig Dis 2012;30 Suppl 2:9-15.

Ono M. Molecular links between tumor angiogenesis and inflammation: inflammatory stimuli of macrophages and cancer cells as targets for therapeutic strategy. Cancer Sci 2008;99:1501-6.

Paik SS, Jang SM, Jang KS, et al. Letpin expression correlates with favorable clinicopathologic phenotype and better prognosis in colorectal adenocarcinoma. Ann Surg Oncol 2009;16:297-303.

Pendyala S, Neff LM, Suarez-Farinas M, Holt PR. Diet-induced weight loss reduces colorectal inflammation: implications for colorectal carcinogenesis. Am J Clin Nutr 2011;93:234-42.

Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371:569-78.

Rickles AS, Iannuzzi JC, Mironov O, et al. Visceral obesity and colorectal cancer: are we missing the boat with BMI? J Gastrointest Surg 2013;17:133-43; discussion p 43.

Rudolph A, Toth C, Hoffmeister M, et al. Expression of oestrogen receptor beta and prognosis of colorectal cancer. Br J Cancer 2012;107:831-9.

Saleiro D, Murillo G, Benya RV, Bissonnette M, Hart J, Mehta RG. Estrogen receptor-beta protects against colitis-associated neoplasia in mice. Int J Cancer 2012;131:2553-61.

Sasaki Y, Takeda H, Sato T, et al. Serum Interleukin-6, insulin, and HOMA-IR in male individuals with colorectal adenoma. Clin Cancer Res 2012;18:392-9.

Saxena A, Chumanevich A, Fletcher E, et al. Adiponectin deficiency: role in chronic inflammation induced colon cancer. Biochim Biophys Acta 2012;1822:527-36.

Uddin S, Bavi PP, Hussain AR, et al. Leptin receptor expression in Middle Eastern colorectal cancer and its potential clinical implication. Carcinogenesis 2009;30(11):1832-40.

Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003;112:1796-808.

Waldner MJ, Foersch S, Neurath MF. Interleukin-6--a key regulator of colorectal cancer development. Int J Biol Sci 2012;8:1248-53.

Yi KW, Shin JH, Seo HS, et al. Role of estrogen receptor-alpha in regulating leptin expression in 3T2-L1 adipocytes. Obesity (Silver Spring) 2008;16(11):2393-2399.

Yoshidome H, Kohno H, Shida T, et al. Significance of monocyte chemoattractant protein-1 in angiogenesis and survival in colorectal liver metastases. Int J Oncol 2009;34:923-30.