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Symposium 3: Obesity-related cancers
Molecular mechanisms linking adipokines to obesity-related colon cancer: focus on leptin

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Obesity is linked to increased risk of colon cancer, currently the third most common cancer. Consequently rising levels of obesity worldwide are likely to significantly impact on obesity-related colon cancers in the decades to come. Understanding the molecular mechanisms whereby obesity increases colon cancer risk is thus a focus for research to inform strategies to prevent the increasing trend in obesity-related cancers. This review will consider research on deregulation of adipokine signalling, a consequence of altered adipokine hormone secretion from excess adipose tissue, with a focus on leptin, which has been studied extensively as a potential mediator of obesity-related colon cancer. Numerous investigations using colon cell lines *in vitro*, *in vivo* studies in rodents and investigations of colon cancer patients illuminate the complexity of the interactions of leptin with colon tissues via leptin receptors expressed by the colon epithelium. Although evidence indicates a role for leptin in proliferation of colon epithelial cells *in vitro*, this has been contradicted by studies in rodent models. However, recent studies have indicated that leptin may influence inflammatory mediators linked with colon cancer and also promote cell growth dependent on genotype and is implicated in growth promotion of colon cancer cells. Studies in human cancer patients indicate that there may be different tumour sub-types with varying levels of leptin receptor expression, indicating the potential for leptin to induce variable responses in the different tumour types. These studies have provided insights into the complex interplay of adipokines with responsive tissues prone to obesity-related colon cancer. Deregulation of adipokine signalling via adipokine receptors located in the colon appears to be a significant factor in obesity-related colon cancer. Molecular profiling of colon tumours will be a useful tool in future strategies to characterise the influence that adipokines may have on tumour development and subsequent therapeutic intervention. Study of the molecular mechanisms linking obesity with cancer also supports recommendations to maintain a normal body weight to reduce the risk of colon cancer.

Adipose: Colon cancer: Adipokine: Leptin: Cytokine

Obesity-related cancer

Obesity levels have increased dramatically over the past decade and are predicted to continue to increase. By 2007, it was estimated that 30–80 % of Europeans were overweight or obese[1]. Obesity is now considered to be a global epidemic. It was estimated in 2008 that around 1·5 billion people were overweight worldwide, with 500 million of these individuals being obese, and as many as 10 % of children were thought to be obese[2]. This has led to intensive research in this area. However, despite this, the trend of rising obesity levels continues with the WHO predicting that about 800 million adults will be obese by 2015[2]. This situation is now well recognised as a major public health concern worldwide with a number of co-morbidities associated with being overweight or obese, such as CVD, hypertension, diabetes and liver disease[3]. However, there is now considerable epidemiological evidence that obesity

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has pathophysiological effects that extend beyond these well-known co-morbidities to include a number of organ-specific cancers[4,5]. In particular, the association with increased risk, development and progression of colon cancer is now well established[4–8].

The epidemiological evidence of links between obesity and cancer was officially endorsed in the last 10-year report from the World Cancer Research Fund and American Institute for Cancer Research[9]. The expert panel judged that the strength of evidence causally relating diet and lifestyle factors, such as body and abdominal fat with the risk of colorectal cancer was convincing[9]. This was further endorsed more recently by the World Cancer Research Fund and American Institute for Cancer Research Continuous Update Project Report on colon cancer[10]. The top three of ten recommendations within the last 10-year report to reduce cancer risk are all linked to obesity[9]. These include maintenance of a normal range of body weight, avoiding a sedentary lifestyle and limiting consumption of energy-dense foods and sugary drinks that promote weight gain[9]. However, despite establishing unequivocal epidemiological evidence of links between obesity and colon cancer, the mechanisms linking obesity and colon cancer remain elusive. In order to identify these mechanisms it is necessary to understand how obesity interacts at the molecular and cellular level.

The epidemiological evidence clearly indicates common factors linking obesity and colon cancer[9,5,11]. Both are associated with consumption of high-energy diets, a sedentary lifestyle, increased age and reduced consumption of fruit, vegetables and fibre[9,5,11]. All these factors influence adipose tissue, now firmly established as the body's largest endocrine organ[12]. These factors have the potential to influence the production of adipose-derived hormones and cytokines from the adipose organ[13–16]. Leptin and adiponectin are two of the most abundant and most investigated adipose-derived hormones. It is now clear that in addition to their traditional roles in energy homoeostasis[17], they are now implicated as potential mediators of the effects of obesity on colon cancer risk[18,19]. Significantly, adipose-derived hormones and adipocytokines are also linked to inflammatory and immune responses[20,21]. These are processes intimately linked with both obesity and colon cancer[22–24].

Adipokine regulation of colon tissue

It has been established that the colon epithelium expresses both isoforms of the adiponectin receptor, *ADIPOR1* and *ADIPOR2*[25] and also leptin receptors[25,26]. This provides support for the potential of adiponectin and leptin to influence regulation of cellular processes within the colon. This epithelial layer is where colon cancer originates[27]. This dynamic tissue layer is very tightly regulated to ensure a balance between proliferation, differentiation and apoptosis during the process of constant renewal of the colon epithelium via proliferating stem cells at the base of these crypts[27]. Disruption of these processes leads to uncontrolled proliferation, loss of apoptotic regulation and uncontrolled tumour growth[27]. Notably insulin receptors are also expressed by the colon epithelium[25] indicating potential cross-talk between metabolic homeostasis, leptin, insulin and adiponectin signalling that are all deregulated in obese individuals.

The role of adipose-derived hormones in regulating the colon epithelium is currently a focus of investigations on links between obesity and colon cancer. Homeostatic regulation of this dynamic tissue layer is implied as well as signalling cross-talk between leptin, adiponectin and insulin signalling pathways. The receptors, expressed throughout normal colon epithelium[25,26], are, no doubt, responsive to leptin and adiponectin produced as a consequence of normal physiological responses to diet and adipose tissue levels. However, the impact of consuming excess energy and a Western-style diet, and the associated increases in adipose tissue levels have the potential to disrupt regulation of signalling in the colon epithelium as leptin increases[17] and adiponectin levels fall[28] with increased obesity. This has the potential to impact on colon carcinogenesis. The following sections address the implications of altered adipokine regulation of colon tissue associated with obesity and potential molecular mechanisms linked to increased risk, development and progression of colon cancer with a focus on the role of leptin.

Mechanisms linking leptin to obesity-related colon cancer: *in vitro* colon epithelial cell line models

Prompted by reports of leptin receptor (both short- and long-form signalling variant) expression by various human epithelial colon cancer cell lines, HT-29, CACO-2, DLD-1, SW480, HCT116, LS174-T and LoVo[26,29,30], studies were initiated to investigate molecular mechanisms linking obesity with colon cancer. It was established that leptin stimulation of cultured colon cell lines led to tyrosine phosphorylation of the leptin receptor[29] and activation of major mitogenic signal transduction pathway elements, p42/44 mitogen-activated protein kinase [26,30], c-Jun N-terminal kinase mitogen-activated protein kinase[31], Src/phosphoinositide 3-kinase/protein kinase B[30,32] and extracellular-signal-regulated kinase[30,33]. Signal transduction mediated via tyrosine phosphorylation of the long-form signalling leptin receptor[29], leading to the activation of signal transduction pathways[26,32,33] possibly drives the observed leptin stimulation of cell proliferation and accompanying DNA synthesis in colon cancer cell lines, such as HT-29 and CACO-2[29]. Leptin is also reported to inhibit apoptosis in human colon cancer cells via processes linked to extracellular-signal-regulated kinase, p38 mitogen-activated protein kinase activation and nuclear translocation of NF-κB[30,34]. Anti-apoptotic effects pertinent to colon cancer may also be linked to observed counteraction of Na-butyrate-induced apoptosis[35].

Notably leptin stimulation of proliferation may be confined to colon cancer cells *in vitro*. Fenton *et al.*[36] reported that normal colon epithelial cells, YAMC ($Apc^{+/+}$), isolated from an immortalised murine cell line model that mimics a variety of genetic mutation in cells that can represent stages of carcinogenesis[37], exhibited reduced proliferation in response to leptin, concomitant with induction

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of apoptosis. Conversely, IMCE ($Apc^{Min/+}$), harbouring a mutation in *Apc*, a 'gatekeeper' gene linked to human colon cancer, exhibit increased proliferation and inhibition of apoptosis in response to leptin. YAMC ($Apc^{+/+}$) mimics normal colon epithelial cells while the mutation in the *Apc* tumour suppressor gene in IMCE ($Apc^{Min/+}$) mimics preneoplastic colon epithelial cells[37]. This provides evidence that leptin stimulates proliferation of colon cells dependent on *Apc* genotype, to induce auto/paracrine signalling cascades of inflammatory mediators and growth factors[36,38,39] that could potentially influence colon carcinogenesis *in vivo*. This provokes speculation on the observed differential effects of leptin, inhibiting proliferation of pancreatic cancer cells, but stimulating proliferation of breast, prostate and oesophageal cell lines *in vitro*[40]. Links to leptin regulation of proliferation and apoptosis were further confirmed by studies using colon stem cell clones[41]. This study also revealed that leptin counteracted the cytotoxic effects of the commonly applied colon cancer drug, 5-fluorouracil[41] and provokes speculation on interactions of diet, adipose-derived hormones and cancer therapies.

Mechanisms linking leptin to obesity-related colon cancer: *in vivo* rodent models

The proposed role of leptin as a growth factor in colon, stimulating proliferation of colon epithelium and inhibiting apoptosis *in vitro* has been conflicted by several studies conducted in rodent models. Leptin failed to promote growth of colon cancer xenografts in nude mice and did not increase intestinal tumorigenesis in ApcMin/+ mice[29]. Mutations in *Apc* predispose the ApcMin/+ mouse to development of tumours in the small intestine and colon[42] via loss of regulation of Wnt signalling. Paradoxically, treatment of rats with leptin, following administration of the colon carcinogen, azoxymethane, reduced formation of azoxymethane-induced aberrant crypt foci (markers of precancerous lesions) in rats[43]. Despite an absence of leptin the mutant mouse strain, *ob/ob*, had increased sensitivity to two colon carcinogens, azoxymethane and *N*-methylnitrosourea[44].

However, recent reports that leptin increases colon tumour growth in obesity subsequent to the initiation of colon cancer[45] provide an illuminating insight on the role of leptin in obesity-related cancer. This study reported that obesity, as a consequence of high fat feeding or genetic mutations leading to deficiencies in leptin signalling, led to increased proliferative activity of normal colonic epithelium[45]. The fact that both high fat feeding, previously reported to increase colon cell proliferation in association with the resulting increased plasma leptin[46], and genetic obesity in mice lacking leptin or functional leptin signalling, implies complex interactions between diet, the adipose tissue and regulation of colon tissue. However, azoxymethane-induced tumours grew more slowly in the leptin-deficient *ob/ob* and leptin-receptor-deficient *db/db* mice[45]. This implies that leptin plays a role in tumour development and progression in addition to other factors associated with obesity. The increased leptin receptor expression in colon tumours of azoxymethane-treated mice is a potential link in the observed differences in tumour growth in mice with functional leptin signalling[45]. Together with the finding that leptin is linked to the activation of Wnt signalling via the leptin receptor signal transducer and activator of transcription 3[45] these results reveal a potential molecular mechanism for obesity-related colon cancer. Uchiyama *et al.*[47] presented evidence recently that leptin receptor signalling is enhanced through signal transducer and activator of transcription 3 activation as human colorectal adenoma-tissue progresses to colon cancer. The study by Endo *et al.*[45] also supports evidence that leptin stimulation of colon cell proliferation and inhibition of apoptosis is dependent on the *Apc* genotype[35,38,39]. Teraoka *et al.*[48] also demonstrated that an obese mouse model KK-A(y) that does have an intact leptin and leptin receptor has higher sensitivity to azoxymethane. However, caution must be applied in interpreting sensitivity to azoxymethane, as mouse strains do differ in sensitivity to this chemical dependent on liver metabolism and DNA repair mechanisms[49,50].

Changes in protein[51] and gene[52] expression profiles indicate a role for leptin in regulating a number of proteins and cellular processes in colon tissues that are associated with pathology and further emphasise links to cellular processes associated with colon cancer. For example, leptin was revealed to induce inflammatory cytokines in colon tissue, IL-6, IL-1b and CXC chemokine ligand 1[52]. These inflammatory cytokines are all implicated in colon carcinogenesis[53–56]. CXC chemokine ligand 1 is expressed by colon epithelium and is up-regulated in colon tumours[56]. In addition to a role in inflammatory responses, CXC chemokine ligand 1 is notable as an angiogenic cytokine expressed by colon epithelial cells[56,57]. This lends further support to *in vitro* studies demonstrating leptin induction of vascular endothelial growth factor-driven angiogenesis and vascular development in preneoplastic colon epithelial cells[58]. The finding that leptin may also up-regulate its own receptor, specifically the long-form signalling receptor[52], is also significant in view of the reports that increased leptin receptors expressed by colon tumours lead to increased tumour growth[45].

Role of leptin in human colon cancer

Substantive studies, outlined above, indicating molecular mechanisms linking leptin with increased risk, progression and development of obesity-related colon cancer have prompted further investigation in human populations and colon cancer patients. Leptin receptors are expressed by normal colon epithelial cells in human subjects[59,60]. Examination of leptin receptors reveals altered patterns of expression in human colon tumours[47,59–61]. Furthermore, it has been proposed that leptin receptor expression provides phenotypic information on colon tumour sub-types and overexpression has been associated with better prognosis[59,60]. High expression of the long-form signalling receptor, ObRb, has been associated with increased age, proximally located tumours, high levels of microsatellite instability and lymphocyte infiltration[59]. Association with

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lymphocyte infiltration is supported by studies in rodents indicating that ObRb may be an immunological marker and that leptin can activate inflammatory gene targets associated with colon carcinogenesis[52] and stimulate inflammatory responses in tumour colonocytes, leading to recruitment of cytotoxic T-cells within the tumour microenvironment[21].

Assessment of leptin signalling in tumour tissue needs further investigation to determine the proposed impact on prognosis. The complexity of this issue is confounded by various aspects associated with leptin production and signalling in human colon cancer patients. Leptin expression is reported to be elevated as tumorigenesis progresses[24,62]. Leptin expression in colon tissue may be positively correlated with tumour features that are associated with improved survival of colorectal cancer patients[62]. However, a study by Stachowicz *et al.*[61] failed to detect the mRNA encoding the leptin protein in samples collected from human colon cancer patients. The impact of plasma leptin is confounded by inconsistent and conflicting data reported from studies on colon cancer patients[47,63–67]. Some studies report reduced levels of serum leptin in colon cancer patients[65,66], while others indicate that increased serum leptin is associated with incidence of colon cancer in men, but not in women[63,64]. Salageanu *et al.*[67] also assert that serum leptin is low in colon cancer patients compared to controls and that levels decreased with tumour progression and aggressiveness[67]. A more recent report failed to determine significant differences in serum leptin in colon cancer cases and controls[47]. Conflicting reports may be due, in part, to cachexia and anorexia that are common in colorectal cancer patients[68]. However, Arpaci *et al.*[69] measured low-serum leptin in colon cancer patients without cachexia or anorexia in a small patient population (thirty-six cases and controls). The observation that colon cancer patients have increased omental fat deposits may also lead to increased localised levels of leptin[70].

Summary and conclusions

It is becoming clear that the promotion of colon cancer by diet and adipose interactions is potentially very important. The recognition of positive and negative leptin receptor tumour sub-types[59,60] indicates the potential for diet and obesity levels to impact on colon carcinogenesis and has implications for prognosis and treatment of individual tumours. Deciphering implications for obesity-related colon cancer and colon cancer patients will require further characterisation of genetic variants attributed to SNP in the *Ob* gene and ObRb or altered regulation of these genes, either as a consequence of mutation or methylation changes to promoter regions, both of which are features of tumours, may also be important. Additionally, serum leptin is commonly assessed in obesity-related cancer studies, but lumenal levels of leptin may be equally significant considering the assertion that leptin induces autocrine/paracrine signalling cascades in colon tissue[39]. Secretion of leptin from omental fat[70] and colon epithelium[24,62] has the potential to impact on leptin receptors in normal and colon tumour tissues. The identification of leptin-regulated genes and cellular processes linked to inflammation[52] and Wnt signalling[38,39] present us with particularly interesting targets for follow-up studies to elucidate links between obesity, leptin and cancer.

Current knowledge lends support to recommendations that cancer survivors maintain a normal body weight and avoid weight gain during treatment for colon cancer[8,18,71]. In summary, it will be important to dissect the mechanisms linking obesity to cancer to determine an individual's risk of developing obesity-related cancers and strategies required to reduce this risk and prevent chemoresistance and recurrence. In order to achieve this it will be important to assess multiple interacting pathways conducted both *in vitro* and *in vivo* to elucidate the complex interplay between diet and adipose tissues and responsive tissues prone to obesity-related cancers.

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References

1. WHO (2007) European Action Plan for Food and Nutrition Policy 2007–2012. Copenhagen: WHO Regional Office for Europe.
2. WHO (2008) Obesity and Overweight. WHO Fact Sheet No. 311. http://www.who.int/mediacentre/factsheets/fs311/en/index.html
3. Guh DP, Zhang W, Bansback N *et al.* (2009) The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. *BMC Public Health* **9**, 88.
4. Calle EE & Kaaks R (2004) Overweight obesity and cancer: Epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* **4**, 579–591.
5. Harriss DJ, Atkinson G, George K *et al.* (2009) Lifestyle factors and colorectal cancer risk: Systematic review and meta-analysis of associations with body mass index. *Colorectal Dis* **11**, 689–701.
6. Giovannucci E, Ascherio A, Rimm EB *et al.* (1995) Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann Int Med* **122**, 327–334.
7. Le Marchand L, Wilkins LR, Kolonel LN *et al.* (1997) Associations of sedentary lifestyle, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer. *Cancer Res* **57**, 4787–4794.
8. Frezza EE, Wachtel MS & Chiriva-Internati M (2006) The influence of obesity on the risk of developing colon cancer. *Gut* **55**, 285–291.
9. World Cancer Research Fund/American Institute for Cancer Research (2007) *Food Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington, DC: AICR.
10. World Cancer Research Fund/American Institute for Cancer Research WCRF/AICR (2010) Systematic Literature Review Continuous Update Project Report. The Associations

between Food, Nutrition and Physical Activity and the Risk of Colorectal Cancer.
11. Potter JD (1999) Colorectal cancer: Molecules and populations. *J Natl Cancer Inst* **91**, 916–932.
12. Kershaw EE & Flier JS (2004) Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab* **89**, 2548–2556.
13. Ostlund RE Jr, Yang JW, Klein S *et al.* (1996) Relation between plasma leptin concentration and body fat, gender, diet, age, and metabolic covariates. *J Clin Endocrinol Metab* **81**, 3909–3913.
14. Fatouros IG, Tournis S, Leontsini D *et al.* (2005) Leptin and adiponectin responses in overweight inactive elderly following resistance training and detraining are intensity related. *J Clin Endocrinol Metab* **90**, 5970–5977.
15. Al-Lahham SH, Roelofsen H, Priebe M *et al.* (2010) Regulation of adipokine production in human adipose tissue by propionic acid. *Eur J Clin Invest* **40**, 401–407.
16. Dutheil F, Lesourd B, Courteix D *et al.* (2010) Blood lipids and adipokines concentrations during a 6-month nutritional and physical activity intervention for metabolic syndrome treatment. *Lipids Health Dis* **9**, 148.
17. Friedman JM & Halaas JL (1998) Leptin and the regulation of body weight in mammals. *Nature* **395**, 763–770.
18. McTiernan A (2005) Obesity and cancer, the risks, science, and potential management strategies. *Oncol* **19**, 871–881.
19. Kelesidis I, Kelesidis T & Mantzoros CS (2006) Adiponectin and cancer: A systematic review. *Br J Cancer* **94**, 1221–1225.
20. Fantuzzi G & Faggioni R (2000) Leptin in regulation of immunity, inflammation and hematopoiesis. *J Leukoc Biol* **68**, 437–436.
21. Abolhassani M, Aloulou N, Chaumett MT *et al.* (2008) Leptin receptor-related immune response in colorectal tumors: The role of colonocytes and interleukin-8. *Cancer Res* **68**, 9423–9432.
22. Sitaraman S, Liu X, Charrier L *et al.* (2004) Colonic leptin: Source of a novel pro-inflammatory cytokine involved in inflammatory bowel disease. *FASEB J* **18**, 696–698.
23. Karmiris K, Koutroubakis IE, Xidakis C *et al.* (2006) Circulating levels of leptin, adiponectin, resistin, and ghrelin in inflammatory bowel disease. *Inflamm Bowel Dis* **12**, 100–105.
24. Koda M, Sulkowska M, Kanczuga-Koda L *et al.* (2007) Overexpression of the obesity hormone leptin in human colon cancer. *J Clin Pathol* **60**, 902–906.
25. Drew JE, Farquharson AJ, Padidar S *et al.* (2007) Insulin, leptin and adiponectin receptors in colon: Regulation relative to differing body adiposity independent of diet and in response to dimethylhydrazine. *Am J Physiol Gastrointest Liver Physiol* **293**, G682–G691.
26. Hardwick JC, Van Den Brink GR, Offerhaus GJ *et al.* (2001) Leptin is a growth factor for colonic epithelial cells. *Gastroenterology* **121**, 79–90.
27. Ponz de Leon M & Di Gregorio C (2001) Pathology of colorectal cancer. *Digest Liver Dis* **33**, 372–388.
28. Arita Y, Kihara S, Ouchi N *et al.* (1999) Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* **257**, 79–83.
29. Aparicio T, Kotelevets L, Tsocas A *et al.* (2005) Leptin stimulates the proliferation of human colon cancer cells *in vitro* but does not promote the growth of colon cancer xenografts in nude mice nor intestinal tumourigenesis in ApcMin/+ mice. *Gut* **54**, 1136–1145.
30. Hoda MR, Keely SJ, Bertelsen LS *et al.* (2007) Leptin acts as a mitogenic and antiapoptotic factor for colonic cancer cells. *Br J Surg* **94**, 346–354.
31. Ogunwobi OO & Beales IL (2007) The anti-apoptotic and growth stimulatory actions of leptin in human colon cancer cells involves activation of JNK mitogen activated protein kinase, JAK2 and PI3 kinase/Akt. *Int J Colorectal Dis* **22**, 401–409.
32. Jaffe T & Schwartz B (2008) Leptin promotes motility and invasiveness in human colon cancer cells by activating multiple signal-transduction pathways. *Int J Cancer* **123**, 2543–2556.
33. Schnabele K, Roser S, Rechkemmer G *et al.* (2009) Effects of adipocyte-secreted factors on cell cycle progression in HT29 cells. *Eur J Nutr* **48**, 154–161.
34. Ogunwobi OO & Beales IL (2007) Cyclo-oxygenase-independent inhibition of apoptosis and stimulation of proliferation by leptin in human colon cancer cells. *Dig Dis Sci* **52**, 1934–1945.
35. Rouet-Benzineb P, Aparicio T, Guilmeau S *et al.* (2004) Leptin counteracts sodium butyrate-induced apoptosis in human colon cancer HT-29 cells via NF-kappaB signaling. *J Biol Chem* **279**, 16495–16502.
36. Fenton JI, Hursting SD, Perkins SN *et al.* (2006) Interleukin-6 production induced by leptin treatment promotes cell proliferation in an Apc (Min/+) colon epithelial cell line. *Carcinogenesis* **27**, 1507–1515.
37. Whitehead RH, VanEeden PE, Noble MD *et al.* (1993) Establishment of conditionally immortalized epithelial cell lines from both colon and small intestine of adult H-2Kb-tsA58 transgenic mice. *Proc Natl Acad Sci USA* **90**, 587–591.
38. Fenton JI, Lavigne JA, Perkins SN *et al.* (2008) Microarray analysis reveals that leptin induces autocrine/paracrine cascades to promote survival and proliferation of colon epithelial cells in an Apc genotype-dependent fashion. *Mol Carcinog* **47**, 9–21.
39. Fenton JI, Hursting SD, Perkins SN *et al.* (2007) Leptin induces an Apc genotype-associated colon epithelial cell chemokine production pattern associated with macrophage chemotaxis and activation. *Carcinogenesis* **28**, 455–464.
40. Somasundar P, Yu AK, Vona-Davis L *et al.* (2003) Differential effects of leptin on cancer *in vitro*. *J Surg Res* **113**, 50–55.
41. Bartucci M, Svensson S, Ricci-Vitiani L *et al.* (2010) Obesity hormone leptin induces growth and interferes with the cytotoxic effects of 5-fluorouracil in colorectal tumour stem cells. *Endocr Relat Cancer* **17**, 823–833.
42. Luongo C, Moser AR, Gledhill S *et al.* (1994) Loss of Apc+ in intestinal adenomas from Min mice. *Cancer Res* **54**, 5947–5952.
43. Aparicio T, Guilmeau S, Goiot H *et al.* (2004) Leptin reduces the development of the initial precancerous lesions induced by azoxymethane in the rat coloni mucosa. *Gastroenterology* **126**, 449–510.
44. Ealey KN, Lu S & Archer MC (2008) Development of aberrant crypt foci in the colons of *ob/ob* and *db/db* mice: Evidence that leptin is not a promoter. *Mol Carcinog* **47**, 667–677.
45. Endo H, Hosono K, Uchiyama T *et al.* (2011) Leptin acts as a growth factor for colorectal tumours at stages subsequent to tumour initiation in murine colon carcinogenesis. *Gut* **60**, 1363–1371 .
46. Liu Z, Uesaka T, Watanabe H *et al.* (2001) High fat diet enhances colonic cell proliferation and carcinogenesis in rats by elevating serum leptin. *Int J Oncol* **19**, 1009–1014.
47. Uchiyama T, Takahashi H, Endo H *et al.* (2011) Role of the long form leptin receptor and of the STAT3 signaling pathway in colorectal cancer progression. *J Oncol* **39**, 935–940.

https://doi.org/10.1017/S0029665111003259 Published online by Cambridge University Press

48. Teraoka N, Mutoh M, Takasu S *et al.* (2011) High susceptibility to azoxymethane-induced colorectal carcinogenesis in obese KK-Ay mice. *Int J Cancer* **129**, 528–535.
49. Sohn OS, Fiala ES, Requeijo SP *et al.* (2001) Differential effects of CYP2E1 status on the metabolic activation of the colon carcinogens azoxymethane and methylazoxymethanol. *Cancer Res* **61**, 8435–8440.
50. Suzuki R, Kohno H, Sugie S *et al.* (2006) Strain differences in the susceptibility to azoxymethane and dextran sodium sulfate-induced colon carcinogenesis in mice. *Carcinogenesis* **27**, 162–169.
51. Padidar S, Farquharson AJ, Williams LM *et al.* (2011) Impact of obesity and leptin on protein expression profiles in mouse colon. *Digest Dis Sci* **56**, 1028–1036.
52. Padidar S, Farquharson AJ, Williams LM *et al.* (2011) Leptin upregulates pro-inflammatory cytokines in discrete cells within mouse colon. *J Cell Physiol* **226**, 2123–2130.
53. Atreya R & Neurath MF (2005) Involvement of IL-6 in the pathogenesis of inflammatory bowel disease and colon cancer. *Clin Rev Allergy Immunol* B, 00, 187–196.
54. Rose-John S, Mitsuyama K, Matsumoto S *et al.* (2009) Interleukin-6 *trans*-signaling and colonic cancer associated with inflammatory bowel disease. *Curr Pharm Des* **15**, 2095–2103.
55. Park EJ, Lee JH, Yu G-Y *et al.* (2010) Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. *Cell* **140**, 197–208.
56. Drew JE, Mayer C-D, Farquharson AJ *et al.* (2011) Custom design of a GeXP multiplexed assay used to assess expression profiles of inflammatory gene targets in colon normal, polyp and tumour tissue. *J Mol Diag* **13**, 233–242.
57. Yang SK, Eckmann L, Panja A *et al.* (1997) Differential and regulated expression of C-X-C, C-C, and C-chemokines by human colon epithelial cells. *Gastroenterology* **113**, 1214–1223.
58. Birmingham JM, Busik JV, Hansen-Smith FM *et al.* (2009) Novel mechanism for obesity-induced colon cancer progression. *Carcinogenesis* **30**, 690–697.
59. Aloulou N, Bastuji-Garin S, Le Gouvello S *et al.* (2008) Involvement of the leptin receptor in the immune response in intestinal cancer. *Cancer Res* **68**, 9413–9422.
60. Uddin S, Bavi P, Hussain AR *et al.* (2009) Leptin receptor expression in Middle Eastern colorectal cancer and its potential clinical implication. *Carcinogenesis* **30**, 1832–1840.
61. Stachowicz M, Mazurek U, Nowakowska-Zajdel E *et al.* (2010) Leptin and its receptors in obese patients with colorectal cancer. *J Biol Regul Homeost Agents* **24**, 287–295.
62. Paik SS, Jang SM, Jang KS *et al.* (2009) Leptin expression correlates with favorable clinicopathologic phenotype and better prognosis in colorectal adenocarcinoma. *Ann Surg Oncol* **16**, 297–303.
63. Stattin P, Lukanova A, Biessy C *et al.* (2004) Obesity and colon cancer: Does leptin provide a link? *Int J Cancer* **109**, 149–152.
64. Stattin P, Palmqvist R, Söderberg S *et al.* (2003) Plasma leptin and colorectal cancer risk: A prospective study in Northern Sweden. *Oncol Rep* **10**, 2015–2021.
65. Bolukbas FF, Kilic H, Bolukbas C *et al.* (2004) Serum leptin concentration and advanced gastrointestinal cancers: A case controlled study. *BMC Cancer* **4**, 29.
66. Kumor A, Daniel P, Pietruczuk M *et al.* (2009) Serum leptin, adiponectin, and resistin concentration in colorectal adenoma and carcinoma (CC) patients. *Int J Colorectal Dis* **24**, 275–281.
67. Salageanu A, Tucureanu C, Lerescu L *et al.* (2010) Serum levels of adipokines resistin and leptin in patients with colon cancer. *J Med Life* **3**, 416–420.
68. Donnelly S & Walsh TD (1995) The symptoms of advanced cancer. *Semin Oncol* **22**, Suppl. 3, 67–72.
69. Arpaci F, Yilmaz MI, Ozet A *et al.* (2002) Low serum leptin level in colon cancer patients without significant weight loss. *Tumori* **88**, 147–149.
70. Moses AG, Dowidar N, Holloway B *et al.* (2001) Leptin and its relation to weight loss, ob gene expression and the acute-phase response in surgical patients. *Br J Surg* **88**, 588–593.
71. Anderson AS & Caswell S (2009) Obesity management – an opportunity for cancer prevention. *Surgeon* **7**, 282–285.

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