



Review

Obesity and Cancer: Existing and New Hypotheses for a Causal Connection



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ABSTRACT

Existing explanations of obesity-associated cancer emphasise direct mutagenic effects of dietary components or hormonal imbalance. Some of these hypotheses are reviewed briefly, but recent evidence suggests a major role for chronic inflammation in cancer risk, possibly involving dietary content. These ideas include the inflammation-induced activation of the kynurenine pathway and its role in feeding and metabolism by activation of the aryl hydrocarbon receptor (AHR) and by modulating synaptic transmission in the brain. Evidence for a role of the kynurenine pathway in carcinogenesis then provides a potentially major link between obesity and cancer. A second new hypothesis is based on evidence that serine proteases can deplete cells of the tumour suppressors Deleted in Colorectal Cancer (DCC) and neogenin. These enzymes include mammalian chymotryptic proteases released by pro-inflammatory neutrophils and macrophages. Blood levels of chymotrypsin itself increase in parallel with food intake. The mechanistically similar bacterial enzyme subtilisin is widespread in the environment, animal probiotics, meat processing and cleaning products. Simple public health schemes in these areas, with selective serine protease inhibitors and AHR antagonists and could prevent a range of intestinal and other cancers.

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Contents

1.	Introduction	15
2.	Obesity and Cancer	15
2.1.	Insulin Resistance.	15
2.2.	Glucagon	16
2.3.	Leptin	17
2.4.	Adipokines.	17
2.4.1.	Adiponectin	17
2.4.2.	Ceruloplasmin	17
2.5.	Fatty Acid Metabolism	17
2.6.	Chronic Inflammation.	18
2.6.1.	TNF- α	18
2.6.2.	IL-6	18
2.6.3.	IRE1	19
2.6.4.	Th17 T Cells	19
2.6.5.	Inflammasomes	19
2.6.	Summary: Existing Hypotheses	19
3.	New Concepts	19

Abbreviations: Akt, protein kinase B; AHR, aryl hydrocarbon receptor; CNS, central nervous system; CRP, C-reactive protein; DCA, deoxycholic acid; DCC, Deleted in Colorectal Cancer; FAS, fatty acid synthase; GCN2, General Control Non-derepressible-2; IGF-1, insulin-like growth factor -1; IGF1BP, insulin-like growth factor binding protein; IL-6, interleukin-6; IRE1 α , Inositol Requiring Enzyme-1 α ; JAK2, janus kinase 2; MAPK, mitogen-activated protein kinase; mTOR, mechanistic (formerly mammalian) target of rapamycin; NF, nuclear factor; ObR, leptin receptor; PI3 kinase, phosphoinositide 3-kinase; STAT3, signal transducer and activator of transcription 3; TNF- α , tumor necrosis factor- α ; VEGF-A, vascular endothelial growth factor-A.

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3.1.	Kynurenines	19
3.2.	Kynurenines and Cancer	21
3.3.	Serine Proteases	21
3.3.1.	Subtilisin	22
3.3.2.	Overall Dietary Consideration	23
4.	Discussion	23
5.	Outstanding Questions	23
6.	Search Strategy and Selection	24
	Author Contributions	24
	Funding Sources	24
	Declaration of Interest	24
	References	24

1. Introduction

The current impact of obesity on public health is a headline concern worldwide, especially since obesity is a significant risk factor for several types of cancer. Obesity is characterized by an excess of body fat considered to be harmful to health and defined by the World Health Organisation as a body mass index (BMI; body weight [kg]/height [m²]) >30 kg/m² (WHO, 2016) (class 1, 30–35, class 35–40, class 3 > 40) with normal values considered as 18.5–24.9 kg/m² and overweight as intermediate values of 25–29.9 kg/m². The term ‘lean’ is occasionally used to refer to weights below 18.5 kg/m². By these criteria around two-thirds of adults aged over 20 years in the USA are currently overweight with a prevalence of obesity of approximately 35% (Ogden et al., 2012), predicted to reach 42% by 2030 in people over 18 years (Finkelstein et al., 2012).

The main driver for obesity is believed to be an overall rise in caloric intake (Swinburn et al., 2009) with a shift towards snacking patterns of eating and increased consumption of high carbohydrate beverages and dietary fat. Low levels of physical activity increase the problem (Cameron et al., 2003) with a significant but poorly understood role of genetic factors (Thorleifsson et al., 2009). Significant consequences of obesity include the medical, economic and social burdens of obesity-related comorbidities such as coronary heart disease, type-2 diabetes mellitus, respiratory disease and cancer (Renehan et al., 2008). Many of the global concerns around the links between environmental factors and diet, nutrition, obesity and cancer are addressed by the World Cancer Research Fund (WCRF) and their various publications (<http://www.wcrf.org/int/policy/our-publications>).

2. Obesity and Cancer

Tumor development involves a local microenvironment which promotes cell proliferation, partly through release of mitogenic signals, and induces cell survival mechanisms as well as the induction of tolerance in cytotoxic host T cells (Hanahan and Weinberg, 2011; Prendergast et al., 2010). Parkin and Boyd (2011) estimated that 5.5% of cancer cases in the UK were related to overweight and obesity while others have claimed that the relative risk of mortality from cancer, attributable to obesity, was approximately 14.2% in men and 19.8% in women (Calle et al., 2003).

The association between obesity and cancer is quite secure in human populations (Arslan et al., 2009; Pischon et al., 2008; Xu et al., 2003) especially with respect to tumors of the gastrointestinal (GI) tract (Zeng and Lazarova, 2012; Zeng et al., 2014) where being overweight carries a 1.5–2.4-fold increase in cancer risk (Moore et al., 2005). The link has also been supported by animal experiments in which obesity and cancer have been modified by dietary means (Nogueira et al., 2012a, 2012b). Several studies have attempted to define the types of cancer most highly associated with obesity, which include breast cancer in postmenopausal women, colon cancer (especially in men), endometrial, esophageal adenocarcinoma, gall bladder and renal cancers (Bhaskaran et al., 2014; Price et al., 2012; Renehan et al., 2008).

Awareness of the role of lifestyle factors in the relationship between obesity and cancer is gaining prominence and will be addressed in a later section. For example, high red and processed meat consumption has been identified as a risk factor for colorectal cancer (Alexander et al., 2011; Huxley et al., 2009; Magalhaes et al., 2012; Norat et al., 2005) and with an increased risk of obesity (Wang and Beydoun, 2009). A role for adipose tissue is also relevant in the case of breast cancer, where a strong association exists between the amount of mammary adipose tissue and collagen (broadly equating with overall breast size), breast cell density and lifetime risk for mammary cancer (Boyd et al., 2007; DeFilippis et al., 2012). This may be related to the inverse expression of CD36, a common membrane protein which plays a role in cell development and intercellular interactions. Lower levels of CD36 in breast tissue lead to an increase in collagen deposition at the expense of adipose tissue, which declines in quantity. The increased collagen to adipose ratio, as seen normally with aging, results in breasts of higher tissue density and increased cancer risk (Boyd et al., 2007; DeFilippis et al., 2012). Further factors influencing breast cancer development via obesity and breast adiposity have included the possible influence of estrogens produced in adipose tissue. These steroids can promote carcinogenesis and add to the lifetime total of estrogen stimulation from oral contraceptives, hormone replacement therapy, and pregnancies (Gerard and Brown, 2017).

2.1. Insulin Resistance

Adipose tissue is an important site of insulin activity, promoting triglyceride storage and inhibiting lipolysis (Choi et al., 2010). There is a strong positive relationship between fasting insulin levels and postmenopausal cancer risk, specifically in non-users of hormone therapy (Gunter et al., 2009) consistent with the view that postmenopausal breast cancer is analogous to obesity-associated cancer resulting from insulin resistance (Bhaskaran et al., 2014; Renehan et al., 2008). Insulin resistance is a feature of obese individuals, accompanied by a high circulating insulin level which is a well-established risk factor for cancer (Kim et al., 2004; Goodwin et al., 2002; Hsing et al., 2001) and which is associated with marked changes in the levels of inflammatory markers (Lee and Lee, 2014).

In a sample of 208 healthy non-obese volunteers, insulin sensitivity was correlated with cancer development over a 6-year period (Facchini et al., 2001). The insulin resistance associated with obesity may be symptomatic of a more profound dysfunction of the insulin/insulin-like growth factor-1 (IGF-1) axis (Kim et al., 2004; Cohen and LeRoith, 2012). Obesity-related insulin resistance and hyperinsulinemia are associated with elevated blood levels of unbound, but not total, IGF-1 protein (Frystyk et al., 1995; Nam et al., 1997) with activation of the insulin and IGF-1 receptors (IGF-1R) triggering transduction pathways which promote tumor growth (Kulik et al., 1997; Parrizas et al., 1997). Obesity-associated insulin resistance gives rise to increased free IGF-1 levels in the postprandial state whereas a reduction of free IGF-1 is observed in lean insulin-sensitive subjects (Ricart and Fernández-Real, 2001). High levels of insulin could dysregulate IGF-1 signalling by their ability to

reduce expression of the hepatic IGF Binding Proteins (IGFBP) (Nam et al., 1997) resulting in increased levels of free IGF. Whether the chronic pattern of postprandial IGF-1 levels is an important factor in the relevance of this protein to obesity remains unresolved, but it could clearly contribute to the obesogenic (and diabetogenic) propensity of modern ‘snacking’ behavior with the frequent consumption of small quantities of foodstuffs, especially those solid and liquid varieties providing high doses of carbohydrate.

Colorectal cancer risk has been associated with increased levels of circulating IGF-1 in men (Ma et al., 1999) although Wolpin et al. (2009) found no link between IGF-1 and colorectal-cancer specific mortality. In addition, a case-control study discovered no association between IGF-1 and premenopausal or postmenopausal breast cancer (Petridou et al., 2000). However, the relative amounts of bound and free IGF present were not clear.

Up-regulation of the insulin and IGF-1Rs has been indicated in cancer (Hellawell et al., 2002; Papa et al., 1990). Both receptors interact with the intracellular insulin receptor substrate 1, which subsequently promotes the phosphoinositide 3-kinase (PI3 kinase)/protein kinase B (Akt) cascade (Myers et al., 1994). This pathway ultimately inhibits programmed cell death (Datta et al., 1997; Kulik et al., 1997). Upon insulin and IGF-1R activation, the intracellular protein Ras stimulates the mitogen-activated protein kinase (MAPK) pathway, which also plays a vital

role in cell proliferation and inhibition of apoptosis (Parrizas et al., 1997; Menu et al., 2004) (Fig. 1).

2.2. Glucagon

Glucagon, the peptide hormone from pancreatic α -cells opposes the actions of insulin by mobilising glucose and inhibiting its utilisation. Analogues of the natural glucagon-mimetic Glucagon-Like Peptide-1 (GLP-1) reduce body mass and help to prevent type-2 diabetes mellitus and cancer development, partly by inhibiting glycogen synthase kinase-3 (GSK-3). This has led to the introduction of non-peptide compounds such as liraglutide into clinical use (Tomlinson et al., 2016). GLP-1 agonists are also likely to act by suppressing the invasion of pro-inflammatory macrophages into adipose tissue (Lee et al., 2012).

The potential links between obesity and carcinogenesis are exemplified by the finding that GLP-1R agonists can inhibit cancer development as well as type-2 diabetes mellitus. Cancer is one of the main causes of death in patients with type-2 diabetes (Nomiya and Yanase, 2016; Yorifuji et al., 2016). GLP-1 agonists can promote cell apoptosis in some tumors and cell lines, thus exhibiting anti-cancer activity, in some cases by inhibiting glycogen synthase kinase-3 (GSK-3) (Koehler et al., 2011). This activity may stem from the ability of GLP-1 agonists to

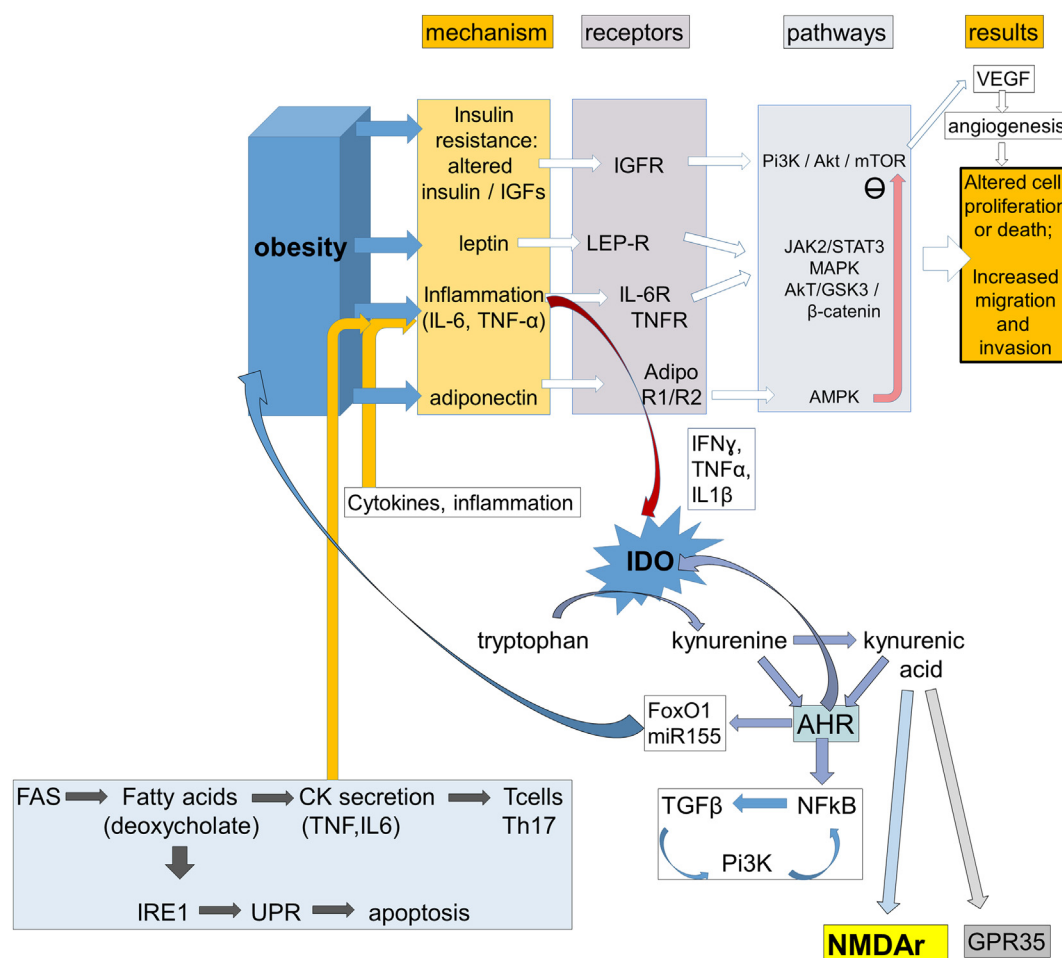


Fig. 1. A schematic illustrating some of the factors proposed to affect obesity and carcinogenesis. Obesity is associated with hormonal and inflammatory changes summarised under “Mechanism” and including insulin resistance. These factors often act via specific “Receptors” which regulate key “Pathways” responsible for the control of cell viability, proliferation, migration and death. The kynurenine pathway is activated by inflammation and acts via the Aryl Hydrocarbon Receptor (AHR) to modulate transcription factors and microRNAs relevant to BMI regulation as well as regulating feedback on inflammation. Kynurenines can affect feeding directly via glutamate receptors (NMDAr) in the brain and possibly via the G-protein coupled receptor GPR35. Fatty acid metabolism can affect inflammatory cytokine production and T cell balance in the immune system.

suppress invasion of adipose tissue by pro-inflammatory macrophages (Lee et al., 2012).

2.3. Leptin

The ability of adipose tissue to generate a factor or factors that increase cell susceptibility to cancer initiation or progression had been supported by a variety of studies on different forms of cancer. Leptin is an adipocyte specific hormone, a product of the *ob* gene involved in regulating food intake and body weight via its actions on the central nervous system (CNS) and adipocytes to suppress appetite and promote metabolism (Halaas et al., 1995). In obese individuals, this hormone is present at higher levels than in their leaner counterparts, positively correlating with an increased proportion of body fat and often associated with leptin resistance.

Epidemiological evidence indicates that high leptin levels are associated with an increased risk of colon cancer (Stattin et al., 2004) and breast cancer (Han et al., 2005; Wu et al., 2009). In agreement with the finding that postmenopausal breast cancer is strongly associated with obesity (Renehan et al., 2008), postmenopausal women with the highest waist circumference and leptin concentration are recognized to have the greatest risk of breast cancer (Wu et al., 2009). However, menopausal status has also been deemed irrelevant to hyperleptinemia-associated breast cancer in one study since there was no correlation between them (Han et al., 2005). Furthermore, Mantzoros et al. (1999) disagreed with the notion that leptin is involved in the etiology of breast cancer, although this study was only conducted on premenopausal women. An increased leptin receptor expression has been identified in several types of cancer (Attoub et al., 2000; Kim, 2009).

Leptin is a stimulator of cell proliferation and tumor growth (Chen et al., 2013; Gonzalez et al., 2006, 2009; Hardwick et al., 2001; Takahashi et al., 1997) probably attributable to MAPK phosphorylation and there is an increased expression of leptin receptors in several types of cancer (Dieudonne et al., 2002; Hardwick et al., 2001). Leptin is a promotor of cyclin D1 (Gonzalez et al., 2006), an important contributor to cell cycle progression, and suppresses apoptosis in ovarian cancer cells (Chen et al., 2013). The activation by leptin of PI3K and MAPK also promotes angiogenesis, contributing to tumor growth (Gonzalez et al., 2006). Additional carcinogenic actions of leptin include increasing aromatase expression leading to enhanced pro-estrogenic pathways, estradiol production and estrogen receptor- α signalling (Catalano et al., 2003, 2004), all of which are of particular significance in estrogen-responsive cancers. Postmenopausal breast cancer is strongly associated with obesity (Renehan et al., 2008). Postmenopausal women with high waist circumference and leptin concentration have the greatest risk of breast cancer (Wu et al., 2009). High leptin levels are also associated with an increased risk of colon cancer.

2.4. Adipokines

In addition to leptin several other adipose-derived factors - adipokines - have subsequently been recognized including adiponectin, tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) (Fain et al., 2004). The expansion of adipose tissue in obesity leads to a rise in the plasma levels of these factors with a reduction in adiponectin production (Arita et al., 1999; Hotamisligil et al., 1995; Vendrell et al., 2004). The incidence of several cancers is increased with elevated circulating leptin and IL-6 levels. (Stattin et al., 2004; Wu et al., 2009) and the risk of colorectal adenomas, which have the potential to develop into carcinomas, have been associated with an increased secretion of TNF- α and IL-6 (Kim et al., 2008).

2.4.1. Adiponectin

Adiponectin is a peptide hormone which has a physiological role in glucose metabolism, enhancing insulin sensitivity and glucose uptake (Berg et al., 2001) as well as stimulating fatty acid oxidation

(Yamauchi et al., 2002). In contrast to other adipokines, adiponectin concentrations are significantly lower in obese individuals compared to those in a normal BMI range (Arita et al., 1999). There is a negative association between circulating adiponectin levels with cancer risk and disease severity (Dal Maso et al., 2004; Goktas et al., 2005; Malvi et al., 2015; Miyoshi et al., 2003; Wei et al., 2005). The reduction in adiponectin secretion seen in obese individuals may contribute to insulin resistance (Yamauchi et al., 2001).

Adiponectin acts on two receptors. AdipoR1 might play a significant role in mediating adiponectin's anti-cancer effects (Nakayama et al., 2008; Pfeiler et al., 2010) although both are expressed in greater quantities in invasive compared with non-invasive breast cancer (Pfeiler et al., 2010). The investigators suggested that low adiponectin levels could induce a feedback loop causing an up-regulation of AdipoR1 expression. In contrast, AdipoR1 levels are lower in several prostate cancer cell lines compared with healthy prostate tissue (Gao et al., 2015). Similarly, primary tumor progression and differentiation of colorectal cancer cells were associated with a reduced expression of AdipoR1 and AdipoR2 (Byeon et al., 2010). Interestingly, Gialamas et al. (2011) found opposing results, demonstrating that AdipoR2 expression was enhanced in advanced tumors and metastatic colorectal cancer cells, with no relationship to AdipoR1 expression. Any mechanistic relationship is therefore complex or influenced by factors not yet identified or understood.

In support of the concept that adiponectin has anti-cancer activity, it has been reported that the hormone has anti-angiogenic properties in vitro (Brakenhielm et al., 2004). Adiponectin inhibits Vascular Endothelial Growth Factor-A (VEGF-A) modulated cancer neo-vascularisation in prostate cancer cells via AdipoR1 and AMPK activation (Gao et al., 2015), strengthening the hypothesis that adiponectin inhibits cancer growth by suppressing angiogenesis (Fig. 1). Sugiyama et al. (2009) discovered that adiponectin inhibits colorectal cancer cell growth in vitro, probably by down-regulating the mechanistic target of rapamycin (mTOR) via AMPK phosphorylation. The dual action of the AMPK up-regulation and Akt inhibition has been considered an important feature of adiponectin's anti-proliferative and pro-apoptotic receptor-mediated effects in malignant cells (Medina et al., 2014). Correlating with these results, adiponectin inhibits the proliferation of breast cancer cells by hindering cell cycle progression, although there is some controversy surrounding the hormone's ability to induce apoptosis (Nakayama et al., 2008).

Adiponectin may also prevent cancer growth by increasing insulin sensitivity (Berg et al., 2001; Yamauchi et al., 2002) as discussed above. Induction of insulin sensitivity would reduce the circulating levels of insulin and IGF-1 which, at high levels of the free form, is believed to be carcinogenic (Goodwin et al., 2002).

2.4.2. Ceruloplasmin

One of the most recently identified adipokines is ceruloplasmin which is highly concentrated in adipose tissue from obese individuals and is synthesized and released at higher rates than in control subjects (Arner et al., 2014). It was estimated that adipose tissue secretion accounted for almost one quarter of the circulating level of the protein. As ceruloplasmin is involved in angiogenesis, its increase presence in obese subjects may facilitate or promote the development of several cancers.

2.5. Fatty Acid Metabolism

Fatty Acid Synthase (FAS) is responsible for catalysing *de novo* synthesis of long-chain fatty acids which are crucial for cellular energy metabolism and membrane function (Wakil, 1989). There is a relationship between increased FAS expression and poor patient prognosis in prostate, colon, breast, gastrointestinal and ovarian tumors (Gansler et al., 1997; Keshk et al., 2014; Rossi et al., 2006). Conversely, inhibiting FAS has proven efficacy in cancer therapy (Kridel et al., 2004; Seguin et al., 2012).

Nguyen et al. (2010) identified a FAS polymorphism which was common in males with higher BMI ranges ($\text{BMI} \geq 25 \text{ kg/m}^2$) and was associated with a greater prostate cancer risk and mortality. Importantly, this correlation was only observed in overweight and obese men, with no association among men of normal weight who possessed this polymorphism. In line with this, tumoral FAS overexpression in obese patients was associated with worse colon cancer mortality rates, in contrast with tumoral FAS overexpression being a sign of improved survival in non-obese patients (Ogino et al., 2008). It was speculated that energy balance might alter the oncogenic influence of FAS upregulation in colon cancer cells, as a hyper-energy state (reflected as the level of adiposity) could augment tumor growth. In contrast, one study concluded that FAS-negative colorectal cancer risk was greater in female patients with a higher BMI, indicating no correlation between BMI and FAS-positive colorectal cancer risk (Kuchiba et al., 2012).

Fatty acids and related microbial products have also been linked with both obesity and cancer (Stone and Darlington, 2017). The compound receiving most attention is deoxycholic acid (DCA), which has been reviewed in previous reports (Balaban et al., 2017; Hara, 2015; Yoshimoto et al., 2013). As noted above, the ability of fatty acids to activate cytokine secretion from macrophages provides a mechanistic link between obesity and inflammation which may be crucial. However, since macrophage and neutrophil activation also enhances the secretion of serine proteases such as chymase, chymotrypsin and cathepsin G, the hypothesis proposed in the following section may also be highly relevant.

2.6. Chronic Inflammation

Chronic inflammation is associated with several non-infective physiological conditions, including obesity (Calle and Kaaks, 2004; Musso et al., 2010; Cottam et al., 2010; George et al., 2017). Local and systemic chronic inflammation have been recognized as states favoring tumor initiation and progression, largely through the generation of pro-inflammatory cytokines, such as $\text{TNF-}\alpha$ and IL-6 (Grivennikov et al., 2009; Morris et al., 2013; Howe et al., 2013). Correlations have been made between local chronic inflammatory conditions, such as inflammatory bowel disease, and an increased risk of developing cancers (Bernstein et al., 2001) while systemic inflammation has been correlated with an increased prevalence of colorectal adenomas. In addition, the presence of obesity was correlated with increased levels of IL-6, $\text{TNF-}\alpha$ and the inflammatory biomarker C-reactive protein (CRP) (Yudkin et al., 1999; Kim et al., 2008). Both $\text{TNF-}\alpha$ and IL-6 are produced by adipose cells (Hotamisligil et al., 1995; Mohamed-Ali et al., 1997) and by macrophages, which typically accumulate in tissues with increased adiposity (Sopasakis et al., 2005; Weisberg et al., 2003). These pro-inflammatory cytokines may then explain the tumor resistance which can be induced by activated macrophages in white adipose tissue (Xu et al., 2003). Adipose tissue contains high concentrations of pro-inflammatory CD4^+ Th1 and CD8^+ cells together with B cells and dendritic cells (DCs) but in addition has high levels of anti-inflammatory Th2 and Treg cells. The net balance is increasingly shifted towards a pro-inflammatory state in tissue from obese individuals (Lee et al., 2014), promoting an oncogenic environment.

There is an apparent paradox here since, despite the recognition that obesity is accompanied by a chronic low-grade state of inflammation, the evidence for a relationship between systemic inflammatory mediators and the occurrence of cancer is less than compelling. Some general links have been identified, especially in colorectal cancer (Ghuman et al., 2017). It is likely, however, that a resolution of this question will be found in a more specific characterisation and categorisation of the mediators and tumors. Thus, associations have been demonstrated between mediators and the type, location, stability and rate of progression of some cancers (Il'yasova et al., 2005). C Reactive Protein (CRP), $\text{TNF}\alpha$ and IL-6 were all correlated with aspects of lung cancer, while CRP and IL6 were correlated with the presence of colorectal cancer and

only CRP showed any relationship to breast cancer, with none of these markers having any association with prostate cancer (Il'yasova et al., 2005). As the range of useful markers of inflammation is expanded, more specific relationships are likely to be revealed with different aspects and properties of cancers (Rasmussen et al., 2017). Concentrations of inflammatory markers are, of course, increased in a range of non-cancerous conditions which may dilute any association with cancer.

There are several areas of overlap between the inflammatory hypothesis and those presented above. A recent examination of visceral adipose tissue (Frasca et al., 2017) has revealed high densities of pro-inflammatory B cells in that tissue, expressing elevated levels of inflammatory markers higher than in splenic B cells. Adipocyte-conditioned medium promoted the increased formation of the inflammatory cells, which also secreted increased amounts of adipogenic factors and chemoattractant chemokines. Together these results imply a substantial pro-inflammatory environment associated with visceral adipocytes which would favor carcinogenesis in an obese host.

Adipose tissue is not merely a resting, storage tissue for excess carbohydrates but it secretes a range of compounds with profound effects on metabolic regulation. Obesity is associated with hyperplasia of the adipocytes which generate abnormally high quantities of free fatty acids. The latter are potent activators of macrophages which generate pro-inflammatory cytokines including IL-1 β , IL-6 and $\text{TNF-}\alpha$ (Howe et al., 2013; Iyengar et al., 2015; Morris et al., 2013). This leads to activation of NF κ B via Akt and ultimately to the activation of aromatase and increased synthesis of estrogen, both of which promote estrogen-dependent breast cancer.

Other molecules able to activate inflammatory T cells are continually being identified. The co-activator molecule OX40, for example, enhances the expression of pro-inflammatory genes and exists at high levels on CD4^+ T cells located within adipose tissue (Liu et al., 2017). The degree of expression on human T cells was correlated with body weight, whereas induced deficiency of OX40 led to weight loss in experimental mice. OX40 may therefore represent a novel inflammatory regulator relevant to obesity and linking this disorder with inflammation-induced carcinogenesis.

2.6.1. $\text{TNF-}\alpha$

$\text{TNF-}\alpha$ expression is up-regulated in parallel with an increase in BMI (Hotamisligil et al., 1995; Kim et al., 2008) although Kern et al. (1995) reported that this relationship did not exist for people in the morbidly obese range. There is also a correlation between circulating $\text{TNF-}\alpha$ levels and the prevalence of colorectal adenomata (Kim et al., 2008). The action of $\text{TNF-}\alpha$ is thought to be limited to the local adipose tissue micro-environment, where it may function in an autocrine and paracrine fashion since it is not released systemically into the vascular system (Mohamed-Ali et al., 1997). This may explain why local changes in $\text{TNF-}\alpha$ levels do not necessarily correspond to variations in systemic $\text{TNF-}\alpha$ concentrations (Hotamisligil et al., 1995).

Functionally, $\text{TNF-}\alpha$ regulates other adipokines and can induce cell survival, promoting oncogenesis. In vitro studies have demonstrated a reduction of adiponectin mRNA levels within adipose tissue in response to $\text{TNF-}\alpha$, an action that would promote tumor progression (Bruun et al., 2003). On the other hand, although it is widely recognized that $\text{TNF-}\alpha$ plays a vital role in inducing tumor necrosis, it is now understood to have anti-apoptotic potential in some tumors, at least partly through the stimulation of nuclear factor- κ B (NF κ B) (Rubio et al., 2006). The precise role of $\text{TNF-}\alpha$ may, therefore, as with other molecules implicated in cancer, be dependent on cell type, cancer stage, local microenvironment and many other factors.

2.6.2. IL-6

The plasma levels of IL-6 in the systemic circulation of morbidly obese patients – a population at risk for cancer related mortality – are significantly greater than control healthy volunteer subjects (Mohamed-Ali et al., 1997; Vendrell et al., 2004; Calle et al., 2003).

Higher levels of IL-6 occur in the blood of patients with ovarian and hepatocellular carcinoma, compared with healthy controls (Porta et al., 2008).

The carcinogenic properties of IL-6 seem to be related to its action via the Janus kinase-2 (JAK2)/Signal transducer and activator of transcription-3 (STAT3) signalling pathway (Fig. 1). This is an essential anti-apoptotic and proliferative mechanism in tumor cells, directly activated by the IL-6 receptor (IL-6R) (Loffler et al., 2007; Wang et al., 2013). In addition, IL-6 stimulation of the PI3K/Akt signal transduction pathway leads to the expression of the cell survival factor cyclin D1 (Wegiel et al., 2008), as well as modulating other intracellular proteins which support tumor growth (Fig. 1). IL-6 also inhibits dendritic immune cell differentiation and promotes immune tolerance, reducing T cell immune-surveillance and cytotoxicity (Menetrier-Caux et al., 1998).

Finally, IL-6 provides intriguing links between insulin and the occurrence of inflammation, since insulin is able to promote IL-6 release into the circulation and induces TNF- α gene expression within adipose tissue (Krogh-Madsen et al., 2004).

2.6.3. IRE1

It is likely that with the recognition of inflammation as a significant precursor of cancerous cell behavior, more factors will be identified which encourage or initiate a local inflammatory response, since they will then become suspects for oncogenesis. A recently described example is the Inositol Requiring Enzyme-1 (IRE-1), an endoplasmic reticular enzyme which responds to imposed cellular stress and high fat content feeding by contributing to activation of the Unfolded Protein Response, a co-ordinated reaction to stress which can lead to macromolecular degradation and apoptosis. It has been shown that in adipose tissue-resident macrophages IRE1 α activation induces a shift in the biomolecular profile of those cells towards a more highly pro-inflammatory (M1) state of polarization (Bujisic and Martinon, 2017; Shan et al., 2017). If this activation is maintained chronically, it could well contribute to the initiation of tumor formation.

2.6.4. Th17 T Cells

The importance of the relative numbers and activity of Th1 and Th2 helper T cells in determining overall inflammatory status is well established, but the discovery of Th17 cells as a subtype of CD4+ effector T cells related to Th1 cells has introduced a new dimension to the field. Th17 cells contribute to the development of inflammation and hyperglycemia, potentiated by B cell activity in obesity-related diabetes (Ip et al., 2016). Using assays on monocytes from subjects with type-2 diabetes mellitus, it has been found that Th17 cells provide the most robust characterisation of the disorder, especially when associated with B cells, while levels of TNF- α were increased in a range of T cell subsets in addition to Th17 cells. Thus, Th17 cells may represent a crucial link between inflammatory status, type-2 diabetes, elevated BMI values, and carcinogenesis (De Simone et al., 2013; Alizadeh et al., 2013). As noted below, the ability of kynurenine catabolites to suppress activation of pro-inflammatory T cells is also likely to make a significant contribution to regulating immune function and cancer risk.

2.6.5. Inflammasomes

The prominent link between inflammation and obesity has been further emphasized by finding that the NLRP3 inflammasome may contribute to the pathology (Stienstra et al., 2010; Vandanmagsar et al., 2011). The NLRP3 proteins are expressed by adipose tissue macrophages whereas mice deficient in the inflammasome exhibit reduced numbers of activated T cells and lower levels of inflammatory cytokines in adipose tissue. Feeding a high-fat diet activates the inflammasome while mice lacking NLRP3 are relatively resistant to the development of obesity following a high fat diet, and show improved insulin efficacy and glucose metabolic control. Inhibitors of NLRP3 might, therefore, be suitable anti-obesity agents.

2.6. Summary: Existing Hypotheses

Overall, the majority of hypotheses proposed over the past 20–30 years have been based around the physiological functions and pathological correlations of compounds intimately involved in general metabolism of adipose tissue or its regulation by systemic factors and the relevance of those compounds to cell proliferation or development that could contribute to abnormal proliferation and migration leading to oncogenesis. The more recently developed concepts to be described below adopt a wider perspective in which the interface between adipose metabolism, inflammation and carcinogenesis is mediated by newly uncovered links involving biochemical pathways which open new perspectives on the obesity/cancer relationship in a more holistic, biologically integrated manner.

3. New Concepts

3.1. Kynurenines

The kynurenine pathway represents the dominant pathway of tryptophan catabolism, accounting for the disposal of around 95% of the tryptophan not used for protein synthesis. It is initiated by the oxidative enzymes indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO) (Chen and Guillemin, 2009; Stone and Darlington, 2002; Schwarcz and Stone, 2017) but, while TDO is primarily a constitutive hepatic enzyme, IDO is induced and activated by interferon- γ which drives the pathway as part of the response to infection and immune system stimulation (Prendergast et al., 2014).

The kynurenine pathway is also driven physiologically by eating. Most foods contain tryptophan and excessive food intake will amplify normal tryptophan catabolism. There is some evidence that tryptophan might mediate feedback changes in food intake, since diets supplemented with tryptophan increase food intake in pigs and show a strong trend to do so in dogs (Fragua et al., 2011). A role for this pathway in feeding behavior is supported by the correlation between levels of kynurenine, kynurenic acid and quinolinic acid with the BMI (Favennec et al., 2015) as well as with increased expression of enzymes along the pathway in adipose tissue from obese human subjects. Enzyme expression was greatest in activated macrophages, consistent with the finding that pathway activation could be induced in adipocytes by pro-inflammatory cytokines. There is strong evidence implicating the kynurenine pathway in the 'metabolic syndrome' and insulin resistance which is one of its major features in many obese individuals (Filho et al., 2018; Oh et al., 2017; Oxenkrug et al., 2017; Rebnord et al., 2017). There is a clear correlation between plasma levels of tryptophan and its metabolites, leptin and BMI (Samad et al., 2017). The altered biochemistry appears to develop with chronic obesity since a high kynurenine: tryptophan ratio is seen in adults but not subjects aged 18 or less (Mange et al., 2014). The increased tryptophan oxidation correlated with abdominal adiposity rather than overall BMI, suggesting that it specifically involved an aspect of fat metabolism – the basis of the metabolic syndrome. The inflammation-induced activation of IDO and its metabolism of tryptophan to kynurenine has been proposed as the major mechanism linking inflammation, depression, type-1 diabetes and obesity (Engin and Engin, 2017; Murfitt et al., 2017; Zhong et al., 2017), partly attributable to the effects of tryptophan metabolites on food craving (Dalkner et al., 2017).

Intriguingly, kynurenine represents an important link with recent studies of the Aryl Hydrocarbon Receptor (AHR) and obesity. The AHR is known to influence food intake and metabolism sufficiently to control body mass in animals fed a diet similar to that of European and North American ("Western") populations – a concept related to the 'cafeteria' diets popular in earlier literature. Conversely, blocking the AHR using specific inhibitors such as CH223191 reduced the development of 'Western diet'-induced obesity in mice, as did deletion of IDO-1 (Moyer et al., 2016, 2017).

Kynurenine itself is an important endogenous activator of the AHR, which also responds to exogenous chemicals (notably the dioxin family of toxins) and is activated by both the TGF β induced NF κ B pathway and by Toll-Like Receptors (TLR2/4) activated by oxidized Low Density Lipoprotein (LDL), which also induces IDO-1. Under the influence of TGF β , the non-canonical activation of NF κ B induces IDO-1 expression as well as increased expression of TGF β . The result is an increased expression of IDO-1 maintained by positive feedback in plasmacytoid DCs (Pallotta et al., 2014a). It has therefore been proposed that it is primarily the kynurenine generated by the TGF β or TLR activation of IDO-1 which activates the AHR and maintains food intake at obesogenic levels (Moyer et al., 2016). Direct activation of the AHR by dioxins and related xenobiotics increase adipocyte proliferation and differentiation as well as the release of inflammatory compounds by mature adipocytes (Arsenescu et al., 2008). This places the AHR in a powerful position to regulate the immune system (Gutierrez-Vazquez and Quintana, 2018). It has been suggested that xenobiotic compounds maintain ongoing activation of the AHR tending to promote diabetes, glucose intolerance and aspects of the metabolic syndrome (Park et al., 2013).

Paradoxically, IDO-1 expression is greatly reduced or absent in the mouse Non-Obese Diabetic (NOD) model of autoimmune diabetes (type-1), but artificial transfection of IDO-1 inhibited the development of diabetes in parallel with a reduced generation of pro-inflammatory cytokines including IL-6 and TNF- α (Pallotta et al., 2014b). This may indicate that the overall relevance of the kynurenine pathway in type-1 diabetes depends on inflammatory status.

Obesity and some associated risk factors such as hypertension, may involve the effects of kynurenines in the central control of adipose metabolism via the modulation of neuronal glutamate receptors, to be discussed next. Adipose tissue activation initiates sympathetic reflexes

which are modulated by glutamate receptors and which include responses to leptin, implying that glutamatergic neural control is located downstream of leptin receptor activation (Cui et al., 2013). Glutamate receptors, especially those sensitive to synthetic N-methyl-D-aspartate (NMDA) may be relevant to obesity since they are present in cerebral regions responsible for appetitive and metabolic regulation. The only known selective endogenous agonist at NMDA receptors is quinolinic acid (Stone and Perkins, 1981) a product of kynurenine metabolism (Stone and Darlington, 2002; Badawy, 2017) (Fig. 2) which has been shown to induce a range of physiological and degenerative changes via the NMDA receptors and which has consequently been implicated in several clinical disorders of metabolism or neuronal function including depression, stroke (Stone et al., 2012a) Huntington's disease (Stone et al., 2012b; Forrest et al., 2010) and cognitive disorders such as schizophrenia (Stone and Darlington, 2002; Stone and Darlington, 2013; Schwarcz and Stone, 2017). The pathway is also involved intimately in early brain development and, as a result, interference with the pathway during embryogenesis can affect brain structure and function (Forrest et al., 2013a, 2013b; Khalil et al., 2014), cognitive and behavioral performance of the postnatal offspring (Notarangelo and Pocivavsek, 2017) as well as functions of other organ systems (Song et al., 2017). Adipose tissue activation initiates sympathetic reflexes which are modulated by glutamate receptors and which include responses to leptin, implying that glutamatergic neural control is located downstream of leptin receptor activation (Cui et al., 2013) and is an important component of the appetitive neural network. In this context, it may be relevant that the glutamate-induced animal model of obesity has proved valuable in explaining several aspects of over-eating and obesity and has helped to understand the role of positive influences such as exercise (Gobatto et al., 2002). The presence of glutamate receptors as a key factor in

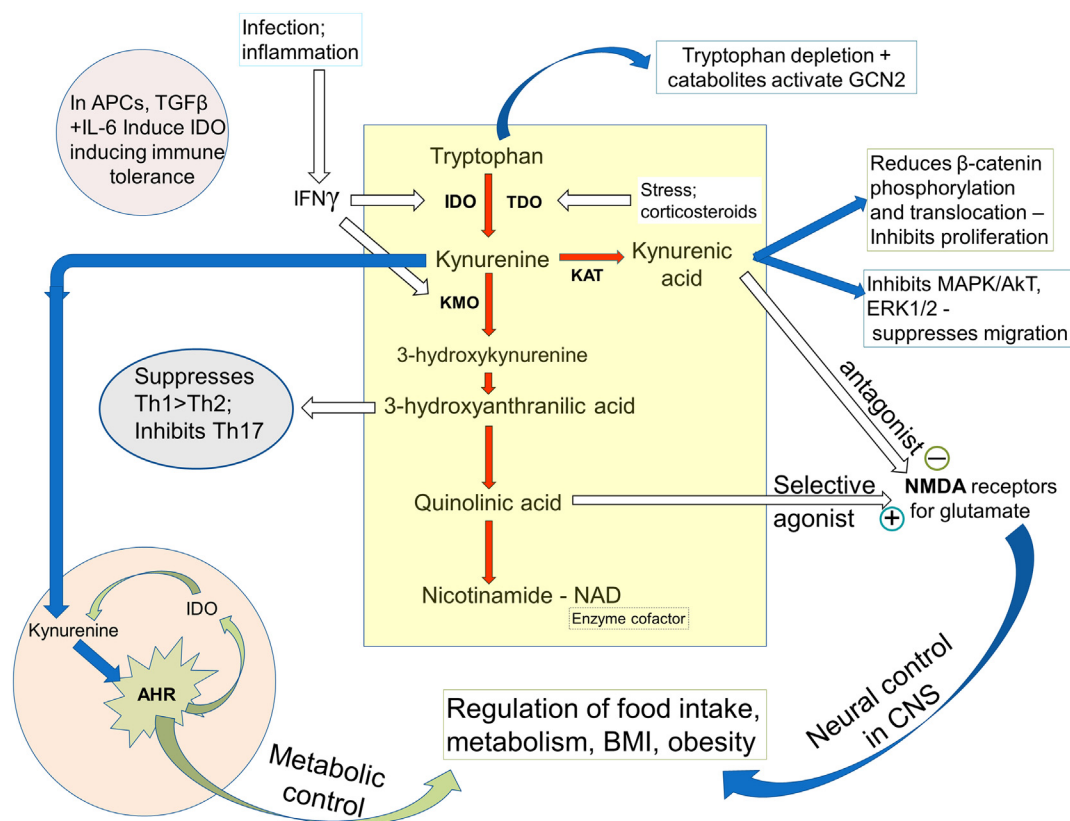


Fig. 2. The kynurenine pathway is initiated by the oxidation of tryptophan via the enzymes IDO and TDO, with downstream catabolites having toxic, antioxidant and cell-protective activity. Several feedback circuits involving the kynurenines, regulation of the Aryl Hydrocarbon Receptor (AHR), T cell production and balance and activity of the cell survival modulator GCN2 place the pathway in a central position to integrate many aspects of metabolic and feeding control. Quinolinic acid as an agonist and kynurenic acid as an antagonist at NMDA receptors contribute to the activity of feeding regulatory systems in the hypothalamus. Effects on β -catenin activation and translocation as well as key enzymes in the determination of cell viability, such as MAPK and ERK1/2 account for the effects of kynurenines on carcinogenesis.

obesity also explains the anti-obesity activity of glutamate antagonists such as memantine (Hermanussen and Tresguerres, 2005).

Importantly, NMDA receptors are blocked by another kynurenine metabolite, kynurenic acid (Perkins and Stone, 1982; Stone et al., 2013). The quinolinic acid activation of NMDAR or their blockade by kynurenic acid could account for part of the regulatory function of kynurenines in feeding behavior and body mass regulation.

3.2. Kynurenines and Cancer

The relevance of the kynurenine pathway is that not only do its components affect the regulation of metabolism, feeding and body mass, largely via the modulation of NMDA receptor activity, but they are also implicated in aspects of carcinogenesis. Expression of the central enzyme of the pathway – kynurenine-3-monooxygenase (KMO) is greater in human hepatic carcinoma cells than controls (Jin et al., 2015) and is known to influence cell proliferation and migration (Lucarelli et al., 2017). A key factor implicating kynurenines in cancer was the discovery that kynurenine was a major endogenous activator of the AHR (Opitz et al., 2011a). Activation of the AHR has been linked to several types of cancer (DiNatale et al., 2010a, 2010b) since it promotes Treg development, suppressing effector T cell activity and promoting tumor development and progression. The importance of this kynurenine–AHR interaction lies partly in its positive feedback nature, since AHR activation induces IDO expression which produces more kynurenine and thus initiates a potentially explosive generation of IDO and kynurenine metabolites.

The kynurenine pathway is known to be up-regulated in triple negative breast cancer (TNBC) cells. This seems to include not only IDO but also the recently described TDO2 whose expression is dependent on NFκB. The increased generation of kynurenine is sufficient to activate the AHR and could contribute to cancer progression and metastasis as noted above. Removal or inhibition of the AHR reduces metastasis, as does the inhibition, *in vivo*, of TDO2 (D'Amato et al., 2015).

The scratch or wound injury assay in culture or *in vivo* is often used to reflect cell migration and is associated with a significant increase in the expression of IDO in the wounded and adjacent cells. However, wound healing has been reported to improve in the absence of IDO or after its inhibition by 1-methyl-D-tryptophan (1MT) (Ito et al., 2015). Tryptophan but not kynurenine improved wound closure, perhaps indicating a role for kynurenic acid. One caveat to consider in all work employing 1MT is that this compound also inhibits tryptophan uptake and upregulates the expression of IDO-1, an action that would counteract enzyme inhibition (Opitz et al., 2011b). On the other hand it has been shown that the transfection of ectopic IDO into fibroblasts, or their treatment with kynurenine, induced less scar tissue than in normal cells (Li et al., 2014). Part of this phenomenon may be explained by kynurenine's ability to induce matrix metalloprotease activity, an action which, interestingly, is dependent on MAPK activity which has also been linked to oncogenesis.

These considerations account for the widespread interest in the development of IDO inhibitors to suppress Treg (and cancer cell) suppression of T effector cells consistent with data that mice develop fewer tumors in the absence of IDO activity (Thaker et al., 2013).

Kynurenic acid levels are lower in many cancer cells than naïve cells, a factor possibly contributing to tumor development since kynurenic acid inhibits cancer cell migration and proliferation albeit at high, micromolar, concentrations (Walczak et al., 2011, 2012, 2014a) probably via inhibition of MAPK, Akt and ERK1/2 (Walczak et al., 2014b). Also, kynurenic acid, as with kynurenine, can suppress inflammation and inhibit the excessive proliferation and overgrowth of regenerating tissue which normally leads to scar formation (Elizei et al., 2015; Poornasjedi-Meibod et al., 2014). Despite these results, kynurenic acid is said to be a good indicator of cancerous tissue with lymphatic metastases (Sagan et al., 2015) although it is often difficult to attribute such correlations to having direct relevance to the cancer itself, rather

than the associated inflammation that exists with advanced, malignant disease.

A different perspective on the kynurenine pathway which is relevant to both the control of body mass and cancer progression is its ability to regulate cells of the immune system. It is well established that kynurenine itself can affect the production of Treg cells as noted above, but it is also metabolized to compounds with marked anti-inflammatory activity. Notably, 3-HAA suppresses the mainly pro-inflammatory Th1 subtype of effector T cells as well as Th17 cells, (Fallarino et al., 2002; Stephens et al., 2013; Criado et al., 2009) with little effect on anti-inflammatory Th2 cells. The generation of tryptophan catabolites such as these, in addition to the metabolic effects of tryptophan depletion can activate General Control Non-derepressible-2 (GCN2) and affect cell proliferation and migration (Eleftheriadis et al., 2015). Overall, the kynurenine pathway is believed to promote a net anti-inflammatory balance in the immune system which would reduce the inflammatory driving force converting some normal or potentially cancerous cells to an actively aggressive state.

Finally, the kynurenine pathway plays an important role in most cells as the synthetic route for nicotinamide and NAD. Depletion of the latter enzymic cofactor is known to suppress cell proliferation and motility by disrupting many fundamental metabolic pathways (Kennedy et al., 2016). Thus, any interference with the activity of IDO or subsequent enzymes in the kynurenine pathway, or a loss of the individual catabolites, is likely to yield similar overall negative effects on cell function. While it is not clear whether such interference would be sufficient to exert significant anti-cancer activity, it is likely that a combination of kynurenine pathway disruption leading to lowered levels of NAD, together with conventional chemotherapy, may have therapeutic advantages.

A major challenge remains in relating kynurenine pathway activity to the initiation of cancer. Some growth factors such as TGFβ are thought to be critical inducers of cell motility and invasion. Certainly TGFβ is a factor initiating EMT (Brito et al., 2015) although equating EMT with cell migration has been cast in to doubt by work indicating a clearer relationship with cancer cell viability and chemoresistance (Fischer et al., 2015; Zheng et al., 2015). Inhibition of IDO (using 1MT) potentiated the induction of EMT by TGFβ, promoting cell migration. This was associated with the recognized molecular markers of EMT such as a loss of E-cadherin and increased expression of N-cadherin.

3.3. Serine Proteases

Serine proteases have been reported to affect a myriad of cellular functions including proliferation and migration, some of which are relevant to inflammation and oncogenesis. Further, serine protease inhibitors can reduce inflammation and the incidence of some tumors (Roy et al., 2010). The molecular mechanisms of these effects, however, have remained unclear but the recent discovery that major, common, mammalian serine proteases such as chymotrypsin and the related bacterial chymotryptic enzyme subtilisin, are able to deplete cells of tumor suppressor proteins (Forrest et al., 2016) has triggered renewed interest in these enzymes and their molecular targets.

The tumor suppressor proteins that were studied included Deleted in Colorectal Cancer (DCC), neogenin (a related protein with 49% structural homology with DCC) and uncoordinated-5 (unc5), all of which are receptors for the extracellular protein family of netrins (Sun et al., 2011a). In the absence of netrins, DCC and neogenin inhibit proliferation and induce apoptosis, resulting in their classification as 'tumor suppressors'. This effect is restrained by netrin binding so that cellular survival and proliferation is dependent on the presence of the netrin-receptor interaction, giving rise to the alternative description of DCC, neogenin and unc5 as 'dependence receptors' (Mehlen and Guenebeaud, 2010). Conversely, in the absence of DCC and neogenin, netrin itself drives proliferation which is normally restrained by the dependence proteins. The consequence of the interplay between these proteins is that loss or

removal of DCC or neogenin will allow increased cell proliferation or migration which will be further enhanced by the unopposed activity of netrin. Hence, there will be a greater probability that the cells affected by the loss of DCC and neogenin will progress to a cancerous state (Fig. 3).

Among the major mammalian serine proteases are the pancreatic digestive enzymes such as trypsin and chymotrypsin. Other serine proteases are produced by the liver (pro-protein convertases), leucocytes (neutrophil elastase) and prostate glands (prostate specific antigen). Chymotrypsin is of special interest since it is extraordinarily stable, being resistant to most other proteases. The concentration of chymotrypsin remains almost unchanged in transit from the pancreas to the feces. Indeed, chymotrypsin is largely responsible for the destruction of another major serine protease, trypsin, whose levels decline progressively between the upper and lower intestines while chymotrypsin is unchanged. In addition, chymotrypsin is absorbed from the intestine into the circulation of humans (Miller et al., 1960; Kabacoff et al., 1963) and laboratory animals (Megel et al., 1964) even after oral administration (Avakian, 1964), giving access of the enzyme to all vascularized tissues. An increased food intake leads to a higher secretion of chymotrypsin (Piccione et al., 2004) to handle the increased digestive demand and which persists into the feces. Over-eating will increase levels of chymotrypsin in the circulation secondary to intestinal absorption. Piccione et al. (2004) reported a correlation in dogs between the concentration of chymotrypsin in the intestinal chyme or feces and body weight. Chymotrypsin levels therefore correlate with body weight (Piccione et al., 2004; Hashimoto and Nara, 2003) whereas elevated serum levels of anti-chymotrypsin are inversely related to body weight (Friis et al., 2002). Conversely, elevated serum levels of anti-chymotrypsin are inversely related to body weight (Friis et al., 2002), consistent with the view that it is increased chymotryptic activity - whether caused by raised chymotrypsin or lowered anti-chymotrypsin - which may be responsible for increased cancer susceptibility. The concentration of chymotrypsin in the human intestine is between 1 and 10 μM , the same concentration range that has been shown to remove the tumor suppressors DCC and neogenin from cellular membranes (Forrest et al., 2016). The concentration of trypsin, in contrast, falls substantially during its intestinal transit.

Over-eating will therefore result in supra-normal levels of chymotrypsin in the intestinal contents (Hashimoto and Nara, 2003). In addition, it was established years ago that chymotrypsin is absorbed from the intestine into the circulation of humans (Miller et al., 1960) and

laboratory animals (Kabacoff et al., 1963; Megel et al., 1964) even after oral administration (Avakian, 1964). Plasma levels will then be increased, giving access of the enzyme to all vascularised tissues. While not identifying the proteins directly, other groups have reported increased circulating chymotryptic activity after increasing intestinal levels (Colman, 1965; Sherry and Fletcher, 1960). In relation to the composition of diet discussed above it is highly relevant that trypsin levels were found to be four times greater in the feces of dogs given a meat-based diet compared with a cereal diet (Merritt et al., 1979).

It is interesting to note that chymotrypsin is able to metabolise insulin (Kono, 1969) raising the possibility that increased levels of chymotrypsin in the plasma and tissues of obese individuals could be at least partly responsible for both the type-2 diabetes and the cancer susceptibility resulting from over-eating.

Finally, it remains unclear whether there is any functional relationship between the chymotryptic activity of the 20S proteasomal subunits - which are targeted by several anti-cancer drugs (Nielsen et al., 2013) - and the chymotryptic activity of subtilisin and chymotrypsin. While proteasomal inhibitors often have little effect against chymotrypsin activity, there is certainly a degree of structural overlap since all these enzymes are inhibited by chymostatin.

3.3.1. Subtilisin

Similar considerations apply to the bacterial chymotryptic serine protease, subtilisin, which is able to deplete DCC and neogenin at nanomolar concentrations in cultured cells, at least an order of magnitude more potent than chymotrypsin (Forrest et al., 2016).

Indeed, just as chymotrypsin concentrations in the blood, determined by its intestinal secretion in proportion to protein intake, may contribute substantially to the obesity-cancer association, the efficacy of subtilisin may represent a major link between environmental factors and cancer. Subtilisin is abundant in the environment and several species of *Bacillus* which secrete subtilisin, including *B. subtilis*, colonise the intestine and, together with their spores, can survive gastric and intestinal digestion (Hoa et al., 2000, 2001; Hong et al., 2008). Subtilisin is also among the proteases used in the preparation of animal feedstuffs and probiotics administered as alternatives to antibiotics (Hoa et al., 2000) to increase meat production in farm animals (Alexopoulos et al., 2004; Kowalski et al., 2009; Sun et al., 2010, 2011b; Ripamonti and Stella, 2009; Hong et al., 2008; Kampf, 2012; Te Giffel et al., 1996) from where the enzyme might enter the human food chain. Numerous studies have revealed the presence of *Bacillus* species in popular food

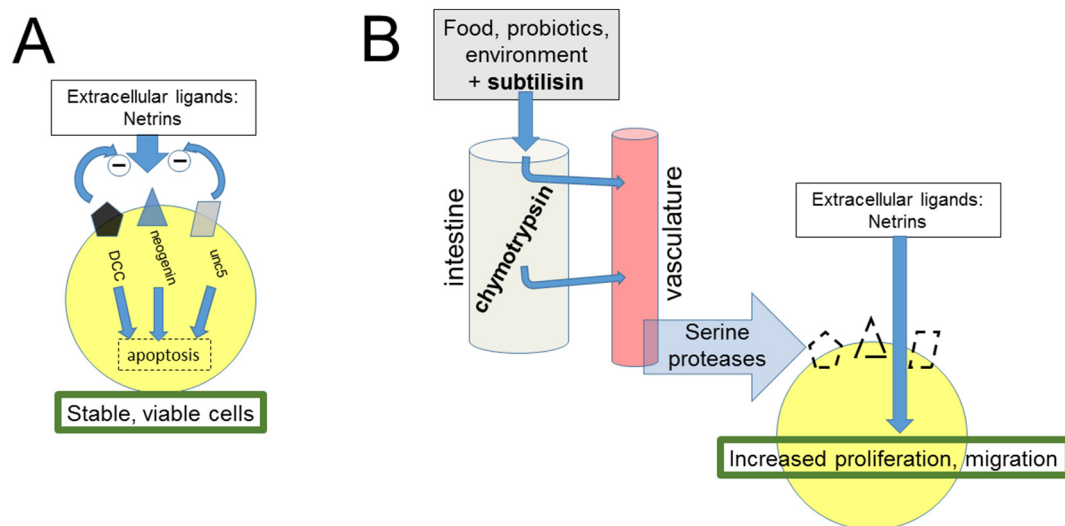


Fig. 3. A. The transmembrane Dependence Receptors Deleted in Colorectal Cancer (DCC), neogenin and unc5 are receptors for the group of netrin ligands. The balance between intrinsic activity of these receptors which induces apoptosis, and the inhibitory effect of netrin binding which also directly promotes cell proliferation, maintains cells in a state of optimum viability. Serine proteases such as chymotrypsin in the digestive tract and systemic circulation, or exogenous chymotryptic enzymes such as subtilisin deplete cells of their Dependence Receptors, allowing netrin to drive proliferation unopposed, potentially leading to carcinogenesis.

items (Cachaldora et al., 2014; Matarante et al., 2004; Te Giffel et al., 1996) and subtilisin-like enzymes are secreted by many other microbes (Bonifait et al., 2011).

This risk is increased by the use of subtilisin in food processing, especially of red meats in which it tenderises the meat and increases its flavor as well as facilitating handling during processing (Piazza and Garcia, 2014; see Stone and Darlington, 2017). These various commercial uses may lead to subtilisin entering the food chain, with tissue levels becoming higher in individuals consuming a high proportion of red meats or processed food. This would be consistent with epidemiological data suggesting that dietary processed red meat is more carcinogenic than fresh produce. A significantly higher risk of several forms of human cancer is associated with regular meat consumption (McCullough et al., 2013; Rohrmann et al., 2013; Key et al., 2002, 2014; Song et al., 2014; Wie et al., 2014; Xu et al., 2014; Xue et al., 2014; Mourouti et al., 2015). Similarly carcinogenesis is increased by beef consumption in experimental animals (Alexander et al., 2011; Aune et al., 2013; Chan et al., 2011; Larsson et al., 2006; Larsson and Wolk, 2006; Norat et al., 2002; Mrkonjic et al., 2009).

Subtilisin is also one of the biological additives included in some domestic cleaning products such as biological washing powders and fluids, with which skin contact and inhalation should be carefully avoided (Gupta et al., 2002; Maurer, 2004). In addition to the innate risks of over-eating and obesity described above, it is probable that increased food intake will increase the total burden of *B. subtilis* and of subtilisin in the gastrointestinal tract, an effect that might be mitigated by increasing transit time. The possibility also requires consideration that increased levels of these serine proteases from different sources, mammalian, environmental and dietary, may result in synergistic effects, further increasing cancer risk. From all these sources, subtilisin and related proteases may represent a significant environmental threat of carcinogenesis.

Conversely, bacteria which generate acidic environments, such as the lactobacilli in some probiotic preparations, should counteract the effects of alkaline proteases such as subtilisin, reducing the latter's ability to deplete cells of their dependence receptors. Such an interaction might contribute to their ability to reduce the incidence of bladder, colorectal and other cancers in humans (Zhong et al., 2014; Davis and Milner, 2009).

3.3.2. Overall Dietary Consideration

Plant-based foodstuffs are generally considered to be protective against cancer (Orlich et al., 2015). Even an early review of 156 studies concluded that cancer risk in people consuming low amounts of fruits and vegetables was approximately double that of individuals with a high intake of these products, even after controlling for potentially confounding factors (Block et al., 1992) and the more recent work referred to above has repeatedly confirmed these findings. The presence in some dietary plant species of the family of Bowman-Birk inhibitors (BBI) provide scientifically credible reasons why diets rich in fruits and vegetables may protect against the development of many cancers.

Bowman-Birk inhibitors are relatively small proteins, highly stable within the intestine and generally resistant to heating and cooking, which are known to be absorbed from the intestine into the blood. Many BBIs are efficient inhibitors of cancer cell growth, giving them both preventative and potentially curative properties even against cancer resistant to conventional anti-cancer medication (Wan et al., 1998, 2002; Kennedy, 1998; Aggarwal and Shishodia, 2006). Their inhibition of serine protease-induced down-regulation of tumor suppressors (Forrest et al., 2016; Stone and Darlington, 2017) could be a key element in this anti-cancer activity.

4. Discussion

Despite the growing awareness of potential mechanisms which could contribute to a causal association between obesity and cancer, their relative importance and details of their molecular basis remain

unclear. Lifestyle factors such as poor diet and low physical activity might facilitate the development of obesity and cancer independently (Norat et al., 2005; Wang and Beydoun, 2009). Simple physical factors such as intestinal transit time, which is known to be relevant to oncogenesis and is reduced with poor diets or low exercise levels, are also likely to be relevant. It is also clear that there are methodological problems associated with the study of these concepts in humans, including doubts about the validity of some forms of measurement. Obesity-associated cancer risk is commonly determined using the measurement of BMI but previous studies imply that more suitable measurements include waist circumference and visceral adiposity (Moore et al., 2004; Pischon et al., 2006). Studies limited to measurements of BMI may be inappropriate, incomplete or even misleading.

Molecular considerations underlying the link between obesity and cancer such as an abnormal insulin/IGF-1 axis, dysregulated hormonal signaling, fatty acid metabolism and chronic inflammation, or a combination of these, could be among the factors involved in carcinogenesis. In addition, we have summarised new information that serine proteases such as chymotrypsin in intestinal secretions and subtilisin in the diet and environment can deplete cells of key tumor suppressors, findings which lead to novel and exciting potential avenues for exploration. These include simple public health measures such as (a) eliminating subtilisin from food processing procedures (b) removing *B. subtilis* and other serine protease generators from farm animal probiotics and, thus, from the human food chain (c) increasing the consumption of fruit and vegetables containing Bowman-Birk and related serine protease inhibitors (d) promoting the thorough cleaning of root vegetables to remove *B. subtilis*-containing soil. There are also non-dietary sources of subtilisin, such as cleaning materials (see ³⁷) and it may be rational to encourage the thorough rinsing of cutlery, crockery and other items used in food preparation and consumption and the thorough rinsing of clothing to remove traces of commercially added subtilisin-like enzymes in biological detergents. Together, these actions might prevent countless incidences of cancer easily and cost-effectively.

What remains unclear is the nature of the relationship between any one of the mechanisms discussed above and the etiology of cancer. The deletion of dependence receptors, for example, does increase proliferation in some cell types and does increase cell migration as expected of an aggressive, potentially metastatic cell (see Stone and Darlington, 2017). That not all cells respond in this way and that the effects are usually small rather than dramatic has been interpreted by some to indicate that these proteins are less important in cancer than might be expected. However, it has been proposed that around six independent steps are required to convert a normal cell into a rapidly proliferating, actively migrating cancer cell (Hanahan and Weinberg, 2011). That would seem to require an extremely rare combination of events. If, however, there are errors of cellular function being induced frequently throughout life, for example by repeated episodes of over-eating or consuming meat and processed products, then a partial loss of DCC or neogenin could lower the threshold for carcinogenesis to occur when one or two of the other factors strikes (e.g. radiation exposure, low vitamin levels, contact with an oncogenic stimulus such as smoking or air pollution). Tomasetti et al. (2017) have recently proposed a closely similar concept in which a *single* necessary but *avoidable* cellular disturbance could promote cancer development if it occurs on a background of a wide range of spontaneous and essentially *unavoidable* factors. If that is the case, the possible role of individual factors such as an obesity-related product, exposure to a toxin or radiation, or contact with a dietary or environmental serine protease, as discussed here, could become critical. Preventing such avoidable concerns might be far more important to cancer prevention than has been recognized.

5. Outstanding Questions

Most of the current ideas have little in common and important questions remain to be answered. Does chronic manipulation of carbohydrate

or lipid metabolism, by dietary or genetic means, affect the incidence of cancer in experimental animals, or can a clearcut answer be obtained by a comparison of human populations in which these factors are already established as a result of local climatic (and therefore agricultural) conditions, habitual consumption, spiritual preferences or other environmental or lifestyle drivers? Is there robust evidence for genetic abnormalities associated with the production, destruction or receptor-mediated actions of compounds such as adipokines, kynurenines, serine proteases or dependence receptors? Also, given the increasing recognition of the prominent role of the microbiome in health and disease, to what extent do the microbiota produce, catabolise, transport or secrete compounds which include, or influence, the endogenous metabolites? And does the answer to that question have implications for a dietary-modulated dysbiosis with the potential for therapeutic intervention by microbial manipulation (antibiotics, biochemical interference, probiotics, etc.) (Li et al., 2009)?

Does pharmacological or genetic manipulation of the kynurenine pathway alter the susceptibility to carcinogenesis? Are different manipulations based on the hypotheses discussed related to specific forms of cancer or their stage and rate of progression?

One important objective should be to differentiate between factors which independently promote obesity or cancer, and those whose primary effect is obesogenic leading to secondary carcinogenesis. Making that differentiation would greatly assist in the clarification of the underlying mechanisms. Of the more recent hypotheses, the kynurenine hypothesis is more likely to fall into the former category, producing a degree of obesity and oncogenesis independently, whereas the serine protease and dependence receptor concept is more likely to reflect the changes in enzyme activity accompanying obesity and leading to the initiation of cancer local and systemic cancers as a result.

6. Search Strategy and Selection

The World of Knowledge and PubMed databases were used for searching. Initial searches were based on general terms intended to provide a wide-ranging overview of the subject. Also word stems were used to capture related items (obes*, overeating, BMI) and (cancer, carcinoma*, tumor*). Selection at this stage eliminated purely data-gathering, statistical and epidemiological studies which contributed little to the generation of conceptual explanations or which did not materially affect our assessment of the acceptance or rejection of potential hypotheses. Titles were trawled for publications with relevance to a wide range of potential molecular mechanisms and key words identified from this process (such as adiponectin, IGF, kynurenine, serine protease, DCC etc.) were then used for further rounds of more focussed searching including abstracts and then full papers. This left a range of studies with relatively clear relevance to major hypotheses and for each of those hypotheses a further search was focused on two or three key-words central to the hypothesis (adiponectin, IRE1, diabet*, etc., combined with kynuren*, quinolinic, chymotryp*, DCC, neogenin, netrin etc.) and with the general terms used initially. The final selection of references to be cited was based on the amount of information contained, the originality of the findings (as opposed to their confirmation or extension), or their direct relevance to the link between obesity and cancer. Since the nature of much of this review is to draw together a range of data which have not been considered related in the past, including some very fundamental aspects of physiology of the serine proteases, it has been necessary to cite some earlier papers. We consider it important to acknowledge such fundamental reports whose potentially critical importance to disease is only now being recognized.

Author Contributions

MM and TWS performed the initial literature searches and prepared the original draft manuscript, which was subsequently read and substantially modified, with the addition of much additional material, by TWS and LGD.

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Declaration of Interest

All authors declare that they have no conflicts of interest with this review.

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