Dietary Fatty Acids in Cancer

Subjects: Oncology

Contributor: Roberta Masella

Colorectal cancer (CRC) is among the major threatening diseases worldwide, being the third most common cancer, and a leading cause of death, with a global incidence expected to increase in the coming years. Enhanced adiposity, particularly visceral fat, is a major risk factor for the development of several tumours, including CRC, and represents an important indicator of incidence, survival, prognosis, recurrence rates, and response to therapy. The obesity-associated low-grade chronic inflammation is thought to be a key determinant in CRC development, with the adipocytes and the adipose tissue (AT) playing a significant role in the integration of diet-related endocrine, metabolic, and inflammatory signals.

Keywords: diet ; inflammation ; immune cells ; fatty acids ; adipose tissue ; obesity ; colorectal cancer ; transcription factors

1. Introduction

It represents a considerable cost to public health and a clinically urgent issue for the population in several countries [1][2]. Excess adiposity is associated with increased incidence of several cancers, including colorectal cancer (CRC), and represents an important indicator of survival, prognosis, recurrence, and response to therapy. CRC is the third most common cancer worldwide and a leading cause of death with burden expected to increase in the coming years (IARC 2020. Specifically, enhanced adiposity, particularly abdominal obesity, is associated with increased CRC incidence, and cancer risk is highly modifiable by diet.

In addition of being an established risk factor for CRC [3], enhanced adiposity is also associated with worse outcomes [4][5], although the detrimental relationship between obesity and CRC is complex and not yet precisely defined. In this regard, it has been postulated that the production, by AT, of a large spectrum of adipocytokines and metabolites, showing proinflammatory and cancer prone features, is of great importance. Furthermore, obesity-related metabolic alterations (i.e., metabolic syndrome, insulin resistance, lipid metabolism impairment, endocrine changes and oxidative stress) may promote CRC occurrence and progression [6].

Diet and excess adiposity can also affect cancer development by influencing tumour surveillance and shaping the host immune response [7]. Indeed, white AT is now recognized as the largest endocrine organ where signals from diet converge, playing a key role in both metabolism and immune system homeostasis [6][8]. Furthermore, a whole set of immune cells, with either proinflammatory (i.e., dendritic and mast cells, M1 macrophages, neutrophils, Th1 CD4 and CD8 T lymphocytes, and B cells) or antiinflammatory (i.e., M2 macrophages, regulatory T (Treg) cells and Th2 CD4 T lymphocytes, and eosinophils) properties, is held in AT, whose polarization profile depends on the health status of adipocytes [9][10].

Growing evidence indicates that a chronic low-grade inflammatory state, called “meta-inflammation”, occurs in metabolically active tissues, including AT, and characterizes obesity, thus contributing to the impairment of immune cell functions, and representing a key determinant in the development of obesity-related morbidities, including CRC [11]. Indeed, the molecular mechanisms underlying inflammation-promoted tumorigenesis or tumour progression have become an important topic in cancer research, and the crucial importance of the AT microenvironment in regulating the dynamic interplay between neoplastic and immune cells has recently emerged [12].

In this regard, fatty acids (FA), introduced with the diet and processed/released by AT, are gaining importance as main actors in this interplay for their capacity to influence both cancer cell proliferation and the host immune response [13]. In general, long-chain saturated fatty acids (SFA) have been associated with inflammatory effects while short-chain fatty acids, derived from microbial fermentation of indigestible foods, exert anti-inflammatory actions [14]. Likewise, ω6 and ω3 polyunsaturated fatty acids (PUFA) have been associated with inflammatory or anti-inflammatory pathways, respectively

[15]. By virtue of their properties, FA have the potential to control host surveillance mechanisms and shape anticancer responses by directly influencing both innate and adaptive immunity and by regulating AT immune and metabolic homeostasis.

The following sections provide an overview of the changes of FA profiles in human AT occurring in obesity and in CRC and of the role played by FA as regulators of inflammation and immune responses, focusing on the molecular mechanisms and TF involved. Non-homogeneous and sometimes contradictory results were found due to the different fat depots analysed or different FA doses and treatment times in intervention studies. Nevertheless, the type of effect (inflammatory versus anti-inflammatory) of specific FA classes was confirmed in all in vitro and in vivo studies. The potential of these molecules to act as a link among diet, AT inflammation, and CRC development is discussed.

2. Fatty Acid Profiles in Obesity and Colorectal Cancer and Their Relationship with Dietary Intake

A preferential accumulation of SFA and monounsaturated fatty acids (MUFA) have been described for SAT and VAT, respectively, in obese individuals, despite a comparable PUFA composition [16][17]. However, the changes in FA composition occurring in obese subjects with respect to normal-weight individuals have been only poorly explored. We reported a marked decrease of the ω3/ω6 PUFA ratio in VAT of obese as compared to lean subjects, despite comparable total content of SFA, MUFA, and PUFA [18]. Palmitoleic (POA) and stearic (SA) acids were also found enriched in SAT and VAT of obese versus lean individuals, in association with a higher stearoyl-CoA-desaturase 1 (SCD1) index [19][20].

A significant correlation between dietary FA intake and FA composition of AT was demonstrated in obese individuals, in particular for oleic (OA), linolenic (LA), and α-linoleic (ALA) acids, and for total ω6 PUFA [21]. Similarly, higher levels of OA were found in SAT of overweight subjects consuming MUFA-compared to SFA-rich diets [22]. Furthermore, unhealthy dietary habits may influence AT-associated and circulating FA profiles contributing to the alteration of metabolic pathways [20][23]. Under obese conditions, AT also expresses high levels of FA synthase, an enzyme responsible for the synthesis of FA from dietary carbohydrates, which in turn induces inflammation [24].

A number of studies analysing the AT composition in CRC-affected individuals have described alterations of FA metabolism and profiles in different fat depots and specific FA profiles have been correlated with the risk of developing CRC [25][26].

As reported for obese subjects, an unbalanced ω3/ω6 PUFA ratio and accumulation of proinflammatory ω6 PUFA (mostly dihomo-γ-linolenic acid DGLA and AA) in AT take place also in CRC subjects, even though differences were described depending on the relative abundance of individual PUFA and fat depots involved [27][28][29][30]. In CRC patients it was evidenced that FA composition of SAT is only slightly affected, while a significant decrease of the ω3 PUFA ALA and stearidonic acid (SDA), along with increased DGLA and AA content, occurs in VAT [29]. Changes in the ω3/ω6 PUFA profile (higher DGLA and docosapentaenoic acid, DPA, versus lower ALA) were conversely reported in SAT from CRC patients in a different study, in association with markers of systemic inflammation [30]. In contrast, some old studies failed to reveal any change in the relative abundance of the different FA in cancer subjects [31][32].

Specifically, we evidenced a decrease in the ω3/ω6 PUFA ratio and an increased content of DGLA and docosatetraenoic acid (DTA) in cancer patients, irrespective of body weight [18][27]. However, when obese and normal weight patients were compared, accumulation of AA was selectively observed in obese CRC subjects with respect to healthy individuals. Conversely, lean patients were found to be characterized by reduced SFA content despite a higher dietary intake [27][20]. The enrichment in proinflammatory FA observed in cancer patients is associated with constitutive signal transducer and activator of transcription (STAT)-3 activation in adipocytes and enhanced release of inflammatory cytokines and chemokines [27].

Changes in lipid metabolism in AT has also been related to tumour progression [33]. In particular, MUFA content in visceral peritumoral fat of CRC patients was associated with advanced disease, whereas similar levels of SFA and PUFA were found irrespective of the tumour stage [33]. At the same time, the SAT content of MUFA has been negatively associated to the risk of developing CRC in epidemiological studies [34], highlighting that the same category of FA (e.g., MUFA) can play different roles in cancer onset/progression depending on the timing and type of AT [33][34].

As with obese individuals, the levels of circulating free FA have been recently found to be increased in CRC patients and associated with cancer risk [35]. Conversely, CRC risk has been inversely correlated to dietary PUFA intake. A growing body of epidemiological evidence has linked to ω3 PUFA-rich diets or ω3 PUFA dietary supplementation to a potential lower risk of CRC, and a recent study definitely correlated fish intake and dietary intake of individual and total ω3 PUFA with lower incidence of CRC [36].

In conclusion, the altered ω3/ω6 PUFA balance in AT and the enrichment in SFA reported in most studies seems to be a common feature of obese and CRC-affected subjects. This could markedly affect the function of AT and distal tissues, such as the intestinal epithelium, as a result of an increased ω6 PUFA-mediated inflammation and a reduced protective effect of ω3 PUFA. The changes in FA profiles in different fat depots sustain proinflammatory microenvironment in CRC patients, supporting a role for both unbalanced dietary intake and alterations in FA metabolism and storage in colorectal tumorigenesis.

3. Fatty Acids and Adipose Tissue Homeostasis

The importance of AT in controlling systemic inflammation has been pointed out in recent years. Due to its endocrine character, alterations in this tissue may lead to various metabolic disorders such as diabetes, cardiovascular and liver diseases, and cancer. In addition, to release these compounds together with a large number of other active factors able to act in an autocrine and paracrine manner [10], has provided a conceptual framework, which helps to understand how unhealthy diets and obesity contribute to the development of several disorders affecting distal organs and tissues.

People with obesity exhibit a general proinflammatory profile. Changes of cytokine/adipokine secretion by adipocytes and the release of free FA by AT couple with dramatic changes in the immune cell repertoire and function shifting the balance of cell subsets and soluble mediators toward a proinflammatory profile [37][38][39]. This results from an altered balance of key transcription factors able to promote inflammation through the induction of molecules such TNFalpha, IL-6, IL-1β, and Toll-like receptor (TLR) 4. These, in turn, exacerbate the inflammatory state [40][41][42] and can promote a favourable microenvironment to CRC onset/evolution [43].

SFA have been shown to negatively affect metabolic functions [44] and to activate inflammatory pathways by acting as ligands of receptors, such as the TLR, involved in the innate immune response. Conversely, endogenous or dietary PUFA are precursors of both pro- and anti-inflammatory lipid mediators [45].

At the same time, adipocytes from SAT and VAT of obese subjects, treated with free FA (i.e., OA, LA, AA, lauric and myristic acids or PA and SA mixtures) showed a proinflammatory cytokine profile [46][47]. Conversely, ω3 PUFA, in particular DHA and EPA, were reported to exert an anti-inflammatory role in whole SAT and VAT and in isolated adipocytes from obese subjects by reducing proinflammatory mediators [48][49][50]. The capacity of pro- and anti-inflammatory PUFA to regulate immune pathways in VAT suggests a role for the altered PUFA composition in shaping immune cell phenotypes in obesity [51]. The ability of dietary PUFA to regulate adipocyte gene expression further elucidates the role of diet in the modulation of AT inflammation, even though the mechanisms responsible of such an effect still need to be clarified.

Several intervention studies have also investigated the role of FA in the control of AT homeostasis. In a clinical trial of obese participants, ω3 PUFA-rich fish oil (FO) supplementation was found to reduce the expression of NLRP3 inflammasome associated genes in AT and circulating IL-18 levels [50]. Among the genes modulated by the consumption of different PUFA sources are those involved in AT inflammation and metabolism, including inflammasome-associated IL-18, IL-1β and IL-1RN, and genes involved in impaired fasting glucose in obese subjects [50][52]. Conversely, no effect on SAT inflammatory genes was exerted by DHA supplementation in obese postmenopausal women [53].

A strong association between AT inflammation and its SFA and MUFA content was also demonstrated [16]. KOBS study carried out on obese individuals showed that surgery-induced weight loss reduces the expression of inflammatory pathways (IL-1β and NF-κB), and unravelled a positive/negative association between inflammation and SFA and MUFA content, respectively, in both SAT and VAT [20]. FADS1/FADS2 genotypes were found able to modify these correlations, both in KOBS and DiOGenes studies, indicating that variants in this gene cluster may influence the interaction between AT FA and tissue inflammation [16][54].

4. Fatty Acids and Immune Cells: Regulation of Transcription Factors, Inflammatory Pathways, and Effector Functions

Obesity is associated with increased numbers and activation levels of specific immune cell subsets responsible for skewing the balance towards a proinflammatory status. AT-associated active molecules, including FA, may represent important determinants in shaping the immune cell phenotype and tissue microenvironment. In particular, the balance of saturated/unsaturated FA and the relative composition of ω3/ω6 PUFA may have significant consequences on immune system homeostasis, acting as an important link between unhealthy dietary habits/obesity and impaired cancer surveillance [55][56][57].

Although only a few studies have focused on FA-mediated immune cell regulation in the context of human AT, the immunomodulatory effects of dietary FA on cells of both innate and adaptive immunity have been investigated in a number of in vivo studies and in in vitro and animal models [58]. The molecular mechanisms and pathways involved are still poorly understood and often show cell type-specific features.

In this section we discuss the human studies that highlighted the immunomodulatory properties of FA following their dietary supplementation and after in vitro/ex-vivo stimulation of immune cells, focusing on the molecular pathways involved.

The role of FA in the regulation of immune/inflammatory response has been investigated in several intervention studies aimed at assessing the effects of consumption of different FA on inflammation-related genes. As discussed above, the analysis of inflammatory response gene expression profiles in AT have generated discordant results mainly due to differences related to the type of body fat depot analysed. Conversely, gene expression profiling of circulating immune cells within the peripheral blood mononuclear cell (PBMC) fraction turned out to have the potential to clarify the molecular effects of FA consumption on human health [59]. In dietary intervention studies, PBMC gene expression profiles have been shown to act as potential biomarkers reflecting metabolic changes in the liver and AT.

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