Dietary fatty acids and adipose tissue inflammation at the crossroad between obesity and colorectal cancer

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Abstract
Excess adiposity, a worldwide-growing pathological condition, is now recognized as a main risk factor for most chronic diseases including colorectal cancer (CRC). Obese subjects show an increased cancer incidence with obesity representing an important indicator of survival, prognosis, recurrence and response to therapy. A low-grade chronic inflammation of metabolically active tissues including the adipose tissue (AT), defined as meta-inflammation, is a main feature of obesity. Fatty acids (FA), the main AT components, are important modulators of inflammation, and the type of FA stored in AT critically affects tissue functions. Their profile within AT mirrors FA dietary intake but also depends on a metabolic control. Obesity, changes in the habitual diet, weight loss or pathological conditions like CRC influence FA profile of AT pointing to these molecules as important actors in AT dysfunction and meta-inflammation, that characterize metabolic diseases and may favor cancer development. Worth of note, diet is receiving growing attention as a main determinant in cancer prevention due to its capacity to modulate immune response and inflammation. Alterations in the balance between different families of FA may contribute to generate a pro-inflammatory profile with deleterious effects on metabolic and immune homeostasis at both local and systemic levels. This review focuses on FA as regulators of human AT inflammation discussing the role of obesity-, diet-, and weight loss-associated changes in FA profile in this process. The relevance of FA composition of AT in linking diet, obesity and CRC will be also reviewed.
INTRODUCTION

The overweight and obesity epidemic represents a rapidly growing health threat in several countries. Excess adiposity is associated with increased incidence of several cancers and represents an important indicator of survival, prognosis, recurrence and response to therapy in many tumors, including colorectal cancer (CRC). The risk of developing CRC is significantly increased in obese subjects, with abdominal obesity being more predictive than overall obesity, and is highly modifiable by diet\(^1\). Dietary habits and excessive adiposity can not only influence cancer growth but also shape host immune response\(^2\). White adipose tissue (AT), now recognized as the largest endocrine organ, plays a key role in metabolic and immune homeostasis\(^3\). This tissue influences many local and systemic physiological and pathological processes by virtue of its capacity to secrete a large number of hormones, cytokines/chemokines/adipokines, extracellular matrix proteins, lipid metabolites and growth factors\(^4\). In condition of chronic positive energy balance, AT undergoes profound modifications including adipocyte expansion, induction of hypoxia, and mitochondrial function alterations that lead to tissue remodeling, inflammation and metabolic dysfunction\(^5\). These events tightly couple with dramatic changes in the immune cell repertoire and functions\(^6,7\) shifting the balance of cell subsets and soluble mediators toward a pro-inflammatory profile. Indeed, growing evidence indicates that meta-inflammation - a chronic low-grade inflammatory state occurring in metabolically active tissues including the AT - characterizes obesity and contributes to the impairment of immune functions, thus representing a key determinant in the development of obesity-related morbidities, including cancer\(^6\).

Evidence suggests that lipids, especially fatty acids (FA), the main components of AT, play an important role not only in obesity development but also in the interplay between excessive adiposity and development of associated diseases\(^5\). Dietary lipids derived from plants and animals encompass FA (saturated, SFA, monounsaturated, MUFA, and polyunsaturated, PUFA), their derivatives including mono-, di-, and triglycerides and phospholipids, as well as sterols such as cholesterol. Among FA, SFA are mainly found in animal food, but a few plant food is also high in saturated fats, such as coconut, coconut oil, palm oil, and palm kernel oil. MUFA can come from both various plant-based (e.g., vegetable oils and nuts) and animal-based sources (e.g., red meats and high-fat dairy products). PUFA are essential FA as they cannot be synthesized from precursors in the diet, and derive primarily from plant-based sources. However, \(\omega_3\) PUFA can also be found in fish oils\(^10,11\).

The type of FA stored in AT, besides adipocyte fat overload, critically affects tissue functions. FA can directly or indirectly modify immune and inflammatory responses by several mechanisms, acting on cell surface and intracellular receptors that control cell signaling and gene expression\(^12,13\). Recent studies have indicated that dietary FA quality rather than quantity has major implications in meta-inflammation development. In fact, FA exhibit either pro- or anti-inflammatory activity depending on their chemical structure\(^11,12\). In general, long-chain SFA have been associated with inflammation while short-chain FA show anti-inflammatory effects\(^14\). On the other hand \(\omega_3\) PUFA favor anti-inflammatory profiles, while \(\omega_6\) PUFA, with a few exceptions, are endowed with pro-inflammatory activity\(^10\). Lastly, the effect of MUFA is more debated, with evidence for either anti-inflammatory or weak pro-inflammatory responses\(^11,13\).

The FA composition of AT is widely considered a marker of medium- and long-term dietary fat intake, with a general agreement that FA content in AT mirrors their relative abundance in the diet\(^13\). However, FA profile in AT also depends on, at a certain extent, a metabolic control. Indeed, different AT sites exhibit different FA compositions\(^16,17\) as well as different rates of FA turnover\(^18\) and active remodeling\(^19\). Furthermore, while some \(\omega_3\) PUFA such as decosahexaenoic acid are preferentially stored, others like...
eicosapentaenoic acid are preferentially released or turned over during lipolysis\cite{19}. More recently, evidence points to a relevant role of enzymes involved in FA metabolism in defining plasma and tissue FA profiles. Human studies indicate that inter-individual variation in desaturase genes is due to both genetic and lifestyle factors, highlighting that the function of these enzymes may influence disease risk\cite{20}.

In the following sections we will overview obesity-, diet-, and weight loss-associated changes of FA profiles by focusing on human AT. The role of FA as potential regulators of inflammation in metabolically active tissues, in particular AT, and as a link between obesity and CRC development will be discussed.

**OBESITY-ASSOCIATED FATTY ACID PROFILES OF ADIPOSE TISSUE AND THEIR RELATIONSHIP WITH DIETARY INTAKE**

Subcutaneous (SAT) and visceral (VAT) white AT depots constitute AT bulk. Their body distribution shows person-to-person variations and depends on several factors such as age, nutrition, sex, and energy homeostasis of the individual AT\cite{21}. VAT and SAT show significant variations in anatomical, cellular, molecular, and physiological characteristics\cite{22} and play different roles in metabolic syndrome development\cite{21}. In fact, excessive VAT accumulation is commonly associated with insulin resistance, markers of oxidative stress and inflammation, high risk of type 2 diabetes (T2D), dyslipidemia, and high mortality\cite{22-25}. Conversely, SAT accumulation is associated with improved insulin sensitivity and lower risk of T2D. Furthermore, metabolically beneficial adipokines (i.e., leptin and adiponectin) are secreted in higher amounts by SAT, whereas pro-inflammatory mediators are more abundantly secreted by VAT, regardless the body weight\cite{22}. Interestingly, in obese subjects, SAT exhibits a higher content of SFA with respect to VAT that instead shows a higher accumulation of MUFA as well as a higher activity of stearoyl-coenzyme A desaturase 16 (SCD16) and SCD18. Conversely, a similar PUFA composition has been reported for both fat depots\cite{16,17}.

Some studies investigated obesity-associated FA profile of AT that can be modified by specific diets, weight loss or in pathological conditions like CRC. However, the patterns of FA accumulation distinguishing lean with respect to obese subjects are poorly known. A summary of the main differences in FA profiles of AT related to fat depot, obesity, weight loss and cancer, are shown in Table 1.

Despite any difference in SFA, MUFA and PUFA (ω3 and ω6) total content in the VAT of lean with respect to obese subjects, a clear-cut decrease in the ω3/ω6 ratio was detected in the latter\cite{26}. Furthermore, analysis of individual members of the ω6 PUFA family unraveled that arachidonic acid content increases in obese subjects with respect to lean while γ linolenic acid, the only member of the ω6 PUFA family endowed with anti-inflammatory activity, decreases in the same subjects\cite{27}. Moreover, a higher palmitoleic acid content and SCD1 index have been reported in SAT of obese vs. lean subjects\cite{28}. Interestingly, our study demonstrated that higher levels of palmitoleic and stearic acids together with a higher desaturation index (i.e., SCD1 Δ9-18) are found in the VAT of obese subjects\cite{29}.

The FA composition of AT reflects not only the dietary intake but also endogenous fat processing. Thus, changing the nature of the fat consumed has a profound influence on the type of FA available to the body and may alter AT composition\cite{30}. In this regard, our most recent data show a higher arachidonic acid dietary intake in obese subjects as well as a higher arachidonic acid content of VAT\cite{27,29}. The relative proportion of some PUFA (i.e., linoleic, α linolenic, eicosapentaenoic and decosahexaenoic acids) as well as of SFA (i.e., palmitic acid) and MUFA (i.e., palmitoleic acid) in SAT was also found to mainly reflect their dietary intake in a large Swedish cohort study of adult men\cite{31}. Likewise higher levels of oleic acid in SAT were observed when overweight subjects received a MUFA- rather than a SFA-rich diet\cite{32}. The association between dietary FA and their composition in specific AT was studied in a cohort of obese subjects from the
Significant correlations were found for oleic, linoleic and α-linolenic acids and for total ω6 PUFA between the subjects’ habitual diet and AT composition. Interestingly, V AT accumulation was positively associated with ω6 PUFA and inversely associated with MUFA and ω3 PUFA. The subsequent assessment of the dietary pattern, AT composition and degree of obesity showed that despite a similar dietary pattern among the groups, overweight and morbidly obese individuals (BMI ≥ 40 kg/m²) have a higher MUFA content than obese subjects (BMI ≤ 40 kg/m²), probably due to differences in SCD1 activity, slightly higher in morbidly obese than in obese subjects. The association between individual FA content and body weight is rather complex due to the fact that distinct FA share dietary sources and metabolic pathways. Furthermore, a complex interplay among lifestyle, bulk intake of nutrients together with the genetic background influences FA composition of AT in addition to their dietary intake. Likely due to this complexity, only few studies investigated the association between specific FA or FA profile of AT with dietary intake, and assessed the effects of changes in FA composition of AT on the health status. Nevertheless, beneficial changes in FA profiles of AT have been observed in response to weight loss, that can potentially contribute to weight maintenance, as well as to modifications of the dietary pattern. Some rather old studies, carried out in small cohorts of subjects, first observed that weight loss, promoted in obese subjects by different low calorie diets (LCD), results in a reduced accumulation of α-linolenic acid in SAT while the content of other FA remained unchanged. This preferential reduction also occurred when LCD were supplemented with canola or linseed oils. These findings strongly suggest that the relative amount of individual FA in AT depends, not only, on

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**Table 1. Fat depot-, obesity-, weight loss- and cancer-related differences in fatty acid profile of visceral and subcutaneous adipose tissue**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>AT localization</th>
<th>FA profile and lipid metabolism enzymes</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>SAT vs. VAT</td>
<td>SFA &gt; total</td>
<td>[16,17]</td>
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<tr>
<td>MUFAs &lt; total</td>
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<tr>
<td>PUFA &gt; total</td>
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<tr>
<td>Enzymes &lt; SCD1/SCD18</td>
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<tr>
<td>Obese vs. lean</td>
<td>VAT SFA &gt; total; &gt; SA</td>
<td>[26,27,29]</td>
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<tr>
<td>MUFAs &gt; total; &gt; POA</td>
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<td>PUFA &gt; total</td>
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<td>Enzymes &gt; SCD1Δ9-18</td>
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<tr>
<td>SAT MUFAs &gt; POA</td>
<td>[28]</td>
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<tr>
<td>Enzymes &gt; SCD1</td>
<td></td>
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<tr>
<td>Weight loss vs. baseline* (Diet)</td>
<td>SAT SFA &lt; total and PA; &gt; SA</td>
<td>[34-37]</td>
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<tr>
<td>MUFAs &gt; POA; &gt; OA</td>
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<tr>
<td>PUFA &gt; ALA and trans-LA; &gt; EPA, DHA, LA, DGLA, AA and DTA</td>
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<tr>
<td>Weight loss vs. baseline* (Surgery)</td>
<td>SAT SFA &lt; total and PA</td>
<td>[38]</td>
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<tr>
<td>MUFAs &gt; total; &gt; OA; &lt;POA</td>
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<td>PUFA &gt; total e3 and e6, EPA, DPA, LA, GLA and AA</td>
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<td>Enzymes &gt; Elongase 3, 5, 6</td>
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<tr>
<td>CC/CRC vs. healthy</td>
<td>VAT SFA &gt; or &lt; total</td>
<td>[26,27,29,45,74,80]</td>
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<tr>
<td>PUFA &gt; total e6, DGLA, AA and DTA; &lt; ALA and SDA; &lt; e3/e6</td>
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<tr>
<td>Enzymes &gt; SCD1Δ9-18; &lt; FASN</td>
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<tr>
<td>SAT SFA Equal total</td>
<td>[72-75]</td>
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<tr>
<td>MUFAs Equal or &gt; total</td>
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<td></td>
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<tr>
<td>PUFA Equal or &lt; ALA; &gt; DPA, AA, GLA and DGLA; equal LA; &lt; e3/e6</td>
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*FA content of SAT versus VAT. *studies analyzing FA profiles in VAT upon weight loss are not present in the literature. *measured as mRNA expression. ALA: α-linolenic acid; AA: arachidonic acid; DHA: decosahexaenoic acid; DGLA: dihomo-γ-linolenic acid; DPA: docosapentaenoic acid; DTA: docosatetraenoic acid; EPA: eicosapentaenoic acid; GLA: γ-linolenic acid; LA: linoleic acid; OA: oleic acid; PA: palmitic acid; POA: palmitoleic acid; SA: stearic acid; SDA: stearidonic acid; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue
the dietary intake but also on the different rates of metabolic reaction that utilize FA as substrates. Subsequent analysis of FA composition after LCD-induced weight loss and 6-month weight maintenance showed a reduction in total SFA, palmitic and palmitoleic acid content that paralleled a concomitant increase of stearic and oleic acids[^37]. Likewise a significant increase in some ω3 (i.e., eicosapentaenoic and docosahexaenoic acids) and ω6 (i.e., linoleic, dihomo-γ-linolenic, arachidonic and docosatetraenoic acids) PUFA was also observed. Furthermore, a specific role of MUFA in weight management and as predictors of weight change was suggested. In fact lower baseline content of MUFA in SAT predicts a better weight maintenance while lower oleic acid accumulation predicts lower weight decrease[^37]. Potentially beneficial modifications in FA composition of SAT have also been observed in a Finnish study upon obesity surgery - a procedure that leads to changes in gut anatomy and diet as well as to weight loss - in combination with rapeseed oil- and fatty fish-enriched diet[^38]. The main findings were a decreased content in SFA, mainly due to palmitic acid decrease, paralleling an increased accumulation of oleic acid in SAT. The metabolic improvement observed after surgery has been attributed not only to weight loss but also to diet-induced changes of endogenous lipid metabolism enzymes. In fact the increased activity of elongase 5 and delta 6 desaturase (D6D), as well as the decreased activity of SCD1 and D5D were strongly associated with weight loss[^38]. Interestingly, with the exception of ω3 PUFA, comparable modifications in FA content were induced by weight loss or lifestyle intervention without surgery[^38].

**DIETARY FATTY ACIDS AS MODULATORS OF ADIPOSE TISSUE INFLAMMATION**

The primary event in the sequence leading to chronic inflammation in AT is metabolic dysfunction of adipocytes, that promotes inflammation via the expression of inflammatory response genes. In spite of the well-known capacity of FA to modulate inflammatory processes and of the observation that specific FA profiles in the AT are associated with a pro-inflammatory condition, only few studies investigated the effects of direct exposure of adipocytes rather than of other cell types within the stromovascular fraction, to different FA on AT inflammation. Contrasting results were some time achieved likely reflecting differences in AT microenvironment, as the stromovascular fraction of AT strongly contributes to shape inflammation being a major source of immune mediators. Nevertheless, these studies shed light on the molecular pathways triggered specifically in adipocytes underlying the pro- or anti-inflammatory effects of FA[^4,6].

*In vitro* studies have reported that SFA stimulate an inflammatory response by the activation of Toll-like receptor (TLR)/NF-κB pathways. Abdominal SAT and VAT adipocytes from obese subjects exposed to free FA (i.e., oleic, linoleic, arachidonic, lauric and myristic acids or palmitic and stearic acid mixtures) show an increased expression of pro-inflammatory cytokines (TNF-α, IL-6 and CCL2[^39,40]). Interestingly the extent of SFA response does not differ greatly between AT explants and isolated adipocytes, highlighting the capacity of the latter to mount an autonomous inflammatory response to environmental factors[^40]. However, the reported activation of TLR pathways by dietary SFA (lauric and palmitic acids) was not confirmed in other studies in SAT explants and adipocytes under different experimental conditions (i.e., FA concentration or degree of endotoxin contamination[^41]).

While SFA were found to stimulate pro-inflammatory responses, ω3 PUFA, in particular docosahexaenoic and eicosapentaenoic acids, have been reported to exert an anti-inflammatory action in whole SAT and VAT as well as in isolated adipocytes from obese subjects by down-regulating the expression of pro-inflammatory mediators (IL-18, CASP-1, IL-1β, CX3CL1, CCL2, TNF-α and IL-6)^[^41-43]. Likewise, our studies demonstrated that docosahexaenoic acid attenuates the VAT adipocyte inflammatory status by reducing STAT3 activation and IL-6 secretion, and up-regulating adiponectin expression, regardless the body weight[^26,27]. Conversely, exposure of VAT adipocytes from lean and obese subjects to arachidonic acid results in a significant up-regulation of phospho-STAT3 and concomitant down-regulation of PPARγ expression as compared to the untreated paired individuals[^26,27]. The observation that obesity-associated FA profile of VAT parallels alterations of the immune cell repertoire in the tissue microenvironment suggests...
a role for VAT PUFA composition in shaping immune phenotypes. ω3 and ω6 PUFA, in particular decosahexaenoic and arachidonic acids, have also been reported to differently influence adipocyte transcriptional program in lean and obese subjects. Among the genes modulated by decosahexaenoic acid are those involved in AT inflammation and metabolism such as FADS1 and FADS2 genes that code for D5D and D6D, respectively, and thus control AT PUFA metabolism. The regulatory action of dietary PUFA on adipocyte genomics adds further evidence for a role of diet in the modulation of obesity-associated AT inflammation.

The role of FA in the modulation of obesity-associated AT inflammation has also been investigated in several clinical trials aimed at assessing the effect of consumption of different FA on the expression of inflammation-related genes in AT. However, some conflicting results have been reported probably due to the large variability in concentration and type of FA used in each intervention, differences among the specific populations investigated, variability in intestinal microbiota among individuals. Moreover, recent studies suggest that the AT response to FA is more complex than originally anticipated, and that the gene expression in AT is site specific suggesting that not all fat depots in the body are controlled in the same manner. The analysis of inflammatory responses in different sites (SAT or VAT, whole AT or isolated adipocytes) may therefore have generated discordant results.

As described for the in vitro studies, the consumption of a SFA-rich diet results in a pro-inflammatory gene expression profile in SAT (i.e., CD16a, IL-1β, IL-6, IL-6R and TNF-α), while MUFA-rich diet or acute post-prandial MUFA intervention lead to different profiles depending on the category of subjects. Indeed in abdominally obese or healthy subjects the majority of regulated genes show anti-inflammatory features, whereas in subjects at higher risk of T2D the post-prandial consumption of MUFA-containing macadamia nut oil evokes an inflammatory response with up-regulation of several inflammatory genes (CCL2, IL-1β, IL-6, IL-6R, TNF-α and TNFRSF1A). These results indicate that MUFA can also exert a pro-inflammatory response, which is greater among subjects with obesity-related diseases as compared to healthy individuals. In line with this evidence, an exacerbated AT post-prandial inflammatory response (NF-κBp65, CCL2, IL-6 and IL-1β) occurs in SAT of metabolic syndrome patients.

The potential benefits of ω3 PUFA consumption on a wide range of AT inflammatory responses have been highlighted in recent studies. In a randomized controlled trial involving severely obese patients (≥ 40 kg/m2), ω3 PUFA supplementation over an eight-week period results in down-regulation of inflammatory genes (CCL2, CCL3, HIF1A, CD40 and IL-6), and up-modulation of the anti-inflammatory adiponectin in SAT, but not in VAT, in comparison with the control group. Additionally, consumption of different sources of fatty fish reduces the expression of AT inflammatory genes including inflammasome-associated IL-18, IL-1β and IL1RN or impairs fasting glucose in obese subjects. Moreover, in a clinical trial (FFAME) involving healthy volunteers and based on eicosapentaenoic and decosahexaenoic acid supplementation, ω3 PUFA showed immune-modulatory and anti-inflammatory capability through the modulation of several inflammatory and specific immune genes during evoked AT inflammation induced by experimental endotoxemia. In contrast to these results, no effect on SAT inflammation was observed neither in overweight to moderately obese adults consuming a diet rich in ω3 PUFA, nor in obese postmenopausal women after decosahexaenoic acid supplementation. Finally, ω3 PUFA (i.e., eicosapentaenoic acid and/or α-lipoic acid) dietary supplementation in addition to weight loss and dietary interventions unravels differences in the expression of genes related to inflammation and immune response in SAT from overweight/obese women. Other clinical evidence demonstrates that weight loss, known to improve obesity-associated low grade inflammation, is linked to changes in AT FA composition, suggesting a specific role of different FA in weight management and control of inflammation.

A strong association between SFA and MUFA AT profiles and AT inflammation was demonstrated by the KOBS study. The results achieved showed that surgery-induced weight loss of obese individuals
reduces the expression of IL-1β and NF-κB pathway and unravels a positive/negative association between inflammation and SFA and MUFA content, respectively, in both SAT and VAT\[^{[16]}\]. These correlations were modified by the FADS1/FADS2 genotype, both in KOBS and DIOGENES studies, indicating that variants in this gene cluster may influence the interaction between AT FA and tissue inflammation\[^{[16,58]}\]. In the same KOBS cohort, Walle \textit{et al.}\[^{[38]}\] measured serum and AT FA composition and AT expression of genes regulating FA metabolism before and one year after obesity surgery, combined with dietary counseling. Interestingly, some of the changes observed in AT FA profile are associated with the expression of elongases and desaturases, key enzymes in FA metabolism\[^{[38]}\]. According to these results, weight loss after bariatric surgery in morbidly obese women\[^{[59]}\] or after LCD in obese premenopausal women\[^{[60]}\] significantly improves the SAT inflammatory and immune profile by decreasing the expression of pro-inflammatory factors while increasing that of anti-inflammatory molecules as well as of genes involved in the regulation of lipid metabolism. Furthermore, the effects of two different LCD among obese women, within the NUGENOB study trial, were determined on SAT mRNA expression level, according to energy deficit and fat to carbohydrate ratio\[^{[61]}\]. Among the transcripts deregulated during the diets are genes involved in lipid, carbohydrate and energy metabolism\[^{[61,62]}\]. In contrast to these results, no changes in adipocyte gene related to inflammation and metabolism were reported in SAT in two cohorts of obese pre- and post-menopausal women after energy-restricted diets\[^{[63,64]}\], although inflammation related biomarkers were reduced systemically\[^{[63]}\].

**ADIPOSE TISSUE INFLAMMATION, FATTY ACID PROFILE AND COLORECTAL CANCER**

AT-associated inflammation promoted by incorrect dietary habits and obesity, under the influence of signals derived from the gut microbial flora, is a main mechanism that may favor CRC development and progression\[^{[65]}\]. Inflamed AT may contribute to tumorigenesis by releasing pro-inflammatory mediators and by modifying the lipid metabolism, which is part of the reprogrammed energy metabolism that characterizes cancer\[^{[66]}\]. In turn, cancer cells have the ability to induce metabolic changes in neighboring adipocytes and to use AT released FA as substrates for their proliferation\[^{[67,68]}\].

A number of studies have analyzed the profiles of FA in AT of CRC patients, in association or not with dietary intake, or have correlated specific FA profiles with CRC risk\[^{[69,70]}\]. Some old studies reported a similar FA profile in healthy and CRC affected subjects\[^{[71,72]}\]. However, despite a comparable consumption of the major dietary components and fat intake between the study groups, an age-associated decrease in unsaturated fat intake was observed only in the CRC group. Conversely, correlation between dietary and AT PUFA:SFA ratio was found in the control but not in the cancer group\[^{[72]}\].

More recently, a general agreement has been achieved on the increased accumulation of pro-inflammatory \(\omega_6\) PUFA (mostly dihomo-\(\gamma\)-linolenic and arachidonic acids) as well as on the unbalanced \(\omega_3/\omega_6\) PUFA ratio in the AT of CRC patients, regardless of tumor subsite, even though differences were reported among studies on the relative abundance of individual PUFA and type of AT involved\[^{[27,73-75]}\]. In particular, a comparison of VAT and SAT FA profiles in colon cancer (CC) patients highlights a decrease of the \(\omega_3\) PUFA \(\alpha\) linolenic and stearidonic acid content, coupled to increased dihomo-\(\gamma\)-linolenic and arachidonic acid content in VAT of CC patients as compared to controls. Conversely, FA composition of SAT in CC subjects is only marginally altered, with increased \(\gamma\) linolenic acid levels\[^{[74]}\]. Although no dietary information was available for the study population, the low \(\omega_3/\omega_6\) PUFA ratio generally observed in AT likely reflects Western dietary habits\[^{[74]}\]. Changes in the \(\omega_3/\omega_6\) PUFA profile (higher dihomo-\(\gamma\)-linolenic and docosapentaenoic acids, vs. lower \(\alpha\) linolenic acid) were also reported in SAT from CRC patients, in association with markers of systemic inflammation\[^{[75]}\]. The altered \(\omega_3/\omega_6\) PUFA balance in cancer patients can markedly affect tissue composition and function as a result of the reduced protective effect of \(\omega_3\) PUFA. Moreover, a CRC-associated increase of total SFA and MUFA content in VAT and SAT, respectively, was also described in some studies\[^{[74]}\].
Although the influence of BMI on the FA changes in CRC-affected subjects was not considered in the above studies, its relevance emerged in our subsequent studies in which the VAT FA composition was analyzed in newly diagnosed CRC patients, sub-grouped in lean and obese according to BMI\(^{[26,27,29]}\). A reduced \(\omega_3/\omega_6\) PUFA ratio as well as an increased content of dihomo-\(\gamma\)-linolenic and docosatetraenoic acids, coupled with STAT3 activation characterize CRC subjects, irrespective of BMI\(^{[26,27]}\). However, compared to healthy individuals, obese CRC patients show a selective accumulation of arachidonic acid in VAT, whereas a lower SFA content is specific of lean CRC subjects despite a higher dietary intake\(^{[27,29]}\). The lack of correspondence between SFA intake and storage in the latter subjects could in part rely on an accelerated SFA to MUFA conversion as suggested by the increased estimated activity of SCD1 \(\Delta 9-18\)\(^{[29]}\). Interestingly, the increased content of pro-inflammatory FA in AT from CRC-affected individuals is associated to an enhanced adipocyte release of inflammatory cytokines and chemokines (IL-6, CCL2, CXCL8) and with the establishment of an immunosuppressive VAT microenvironment\(^{[27]}\).

AT and its FA content have also been related to tumor progression by Mosconi et al.\(^{[76]}\), who analyzed VAT peri-tumoral fat composition in CRC patients at different tumor stages. The total content of MUFA in close proximity of, but not far from the tumor lesion, was found significantly increased in patients at higher tumor stage, especially stage IV. Comparable levels of SFA and PUFA were instead found in the same patients, irrespective of the tumor stage, suggesting a selective involvement of MUFA in cancer progression\(^{[76]}\). Some food processing techniques (industrial hydrogenation of fats) and cooking methods (heating and frying at temperatures > 220 °C) convert FA, naturally present in food in the cis form, into their trans form, and the latter configuration has been associated with increased risk of cancer and cardiovascular diseases\(^{[77]}\). In the EURAMIC epidemiological study the FA composition of SAT samples was used as a measure of FA intake and associated with CC risk\(^{[78]}\). Statistically significant inverse correlations were found between cis-MUFA concentration and the incidence of CC. Conversely, CC incidence positively correlates with the content of trans-MUFA\(^{[76]}\). As it stems from these results, the same category of FA (e.g., MUFA) can exert a protective or promoting effect on CRC onset/progression, depending on their configuration, the fat depot in which they are enriched, and the tumor stage\(^{[76,78]}\).

As stated above, AT FA profiles are influenced also by the activity of enzymes driving FA synthesis and/or conversion. The expression/activity of these enzymes have been found dysregulated in tumor and AT from cancer patients. In particular, FA synthase (FASN), a key anabolic enzyme, increases in the intestinal mucosa of subjects with CRC or with pre-cancerous lesions according to the increased metabolic demand of cancer cells\(^{[79]}\). In contrast, FASN expression and activity are significantly reduced in VAT adjacent to the tumor lesion, resulting in impairment of FA synthesis and AT storage\(^{[80]}\). The inflammatory VAT microenvironment might account for this reduction as a comparable FASN downregulation was described in obese and CRC-affected individuals\(^{[27,45,81]}\).

Altogether, the alterations of FA metabolism and profiles in different fat depots, in proximity or far from the tumor lesions, contribute to maintain a pro-inflammatory microenvironment in CRC patients, and strongly support a role for both unbalanced dietary intake and changes in FA metabolism and storage in colon and rectal carcinogenesis.

**CONCLUSION**

The type of daily consumed dietary fat together with metabolic activities influence the FA profile in AT and can alter its functionality thus contributing to the onset of meta-inflammation that characterizes obesity and metabolic diseases [Figure 1]. The promotion of inflammatory processes within AT determines an inflamed microenvironment that can represent a trigger for the development of a number of obesity-related pathologies including CRC. All together these findings highlight the relevance of maintaining healthy dietary habits and the central role of AT in preserving health and well-being. However, the studies,
especially the clinical trials, carried out until now provide often contrasting results. This should drive to implement new researches specifically addressed to clarify the relationship among the various molecular pathways involved in FA metabolism and inflammation establishment. The improvement of knowledge on the real role that dietary habits play in modulating key metabolic processes, will allow to provide personalized nutritional advices that take in account the inter-individual differences, including those gender-related, in the response to diet.

DECLARATIONS
Authors’ contributions
Made substantial contributions to conception and design of the review: Conti L, Del Cornò M, Gessani S
Contributed to the literature search, revision and editing of this manuscript: Scazzocchio B, Varì R, D'Archivio M, Varano B
Made substantial contribution to discussion: Masella R

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All authors declared that there are no conflicts of interest.

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