INTRODUCTION

The great concern of cancer worldwide is expanding its shadows to scientific fields previously far from a forthright relation with oncology. Besides to the awareness that malnutrition and some incorrect dietary habits and lifestyles are possible triggers for cancer onset, current literature is moving its spotlight on the fundamental role exerted by the different adipose tissues in this regards [1-3]. The adipocyte is a highly complex cell, despite its simplistic image of a fat-collecting tank. Current evidence is emerging about the fundamental role of the adipocyte as the master tuner of tissue homeostasis, cross talking with resident immunity and stem cells, where even long non coding RNAs might have a major regulatory commitment [4-7]. In this context, oxidative stress has been long time considered a leading factor in carcinogenesis [8]. Furthermore, the relationship between nutrition intake, dietary habits and different lifestyles with oxidative burden and stress response has been widely and thoroughly addressed so far [9]. The relationship between obesity and cancer might be an interesting vanishing point to focus onto the real function of the different adipose tissues in humans.

A first question may regard which relationship does exist between adipose tissue, metabolism and cancer. This issue is of the utmost importance to shed light on the actual role exerted by different dietary habits on cancer onset and development. The relationship between diabetes and cancer is particularly striking [10,11]. Actually, obese subjects are particularly at risk for...
cancer ethiopathogenesis, though controversial opinions were also forwarded [12-16]. This evidence would suggest that the role of adipocytes in this context is particularly striking. Interestingly, due to their lipid storage, adipocytes might be even considered as strays in the cancer pathogenesis. Adipocyte-derived lipids may change cancer drug resistance [17] and noteworthy free fatty acids from the adipose tissue are important biomarkers for cancer, as they elicit or even modulate an immuno-inflammatory response [18-20]. Yet, the role of fats in our complex biology and physiology is not so trivial as suspected only few decades ago and therefore even human daily diet to prevent cancer, when addressing fats, should not follow any prejudicial and widespread fashion about fats in the diet, as fats are powerful regulators of the complex cross talk adipose tissue-immunity-tissue turn over. The role of fat molecules, particularly short chain fatty acids, polyunsaturated fatty acids (PUFAs) and more, are currently emerging as fundamental molecules in men’s health, as cancer preventive substances [20-24]. The complete, though complex, picture that is emerging from current literature is that the adipocyte is at the crossroad of a regulatory network, linking immunity, stress response and cell cycle (with the consequent associated stem mechanisms), where lipids and reactive oxygen species (ROS) act as major signaling molecules. Briefly speaking, the participation of lipids and ROS in creating a master tuner of tissue homeostasis, the leading mechanism that, once disturbed or impaired may cause cancer, is no less fundamental than cytokines and growth factors [25-29]. This overview strongly suggests that lipids intake in the daily diet must be only highly monitored and regulated, not quite completely removed, as the commonest opinion about diet habits would encourage. Particularly for men’s health, an unbalanced diet provided with an excess of protein intake, exceeding the Recommended Dietary Assumptions, alongside with poor fats introduction, can be a potential risk for carcinogenesis, although this evidence yet needs to be further assessed [30-33]. For example, a low protein intake, both from animals and plants, in an isocaloric diet, without necessarily following a low-carbohydrate nutritional panel, decreases cancer risk due to a depletion in the CD8+ T cell and antigen presenting cells, mounting an anti-immune response and lowering the inflammatory reaction. This occurrence is related to the triggering of an unfolded protein response in cancer cells, a mechanism ignited via the activation of the inositol requiring enzyme 1-alpha and retinoic acid inducible gene 1 signaling pathway, resulting in an anti-cancer activity [33].

The role of diet in tuning the adipose tissue function is of the utmost importance. This role is closely associated with further two major components in men’s health, namely the gut microbiome brain axis and the musculoskeletal system. The relationship between the skeletal muscle fiber and the adipocyte is emerging in the very recent years, through the role of myokines [34]. The muscle secretome has an important role in modulating the aforementioned role of the adipose tissue in tuning the mechanism of tissue homeostasis, where molecules, such as brain-derived neurotrophic factor and interleukin (IL)-6 directly participate in the AMP-activated protein kinase-mediated lipid oxidation [34]. In this context, even the turn over of ROS is addressed to regulate muscular optimal activity and cell survival, contrarily to the widespread opinion that ROS are deleterious despite their signaling function [35]. Therefore, the synoptic picture we might draw from this perspective is that oxidative stress and nutrients such as fats are collectively bridled to be used as signaling elements for the complex cross talk with tissues that the adipose tissue exerts in its main function.

In this review I am going to deepen and discuss this issue.

A NOVEL HYPOTHESIS ABOUT THE INTRIGUING ROLE OF THE ADIPOSE TISSUE (THE FUNCTIONAL METASTABILITY OF THE ADIPOCYTE)

So far, the role of the adipose tissue, and consequently of the adipocyte as its key cell model, has been ultimately confined to the trivial image of a fat reservoir, with the only fundamental purpose to modelling anatomic regions as a sort of “plastic wax”. However, in recent years this commonly widespread view on the adipose tissue has been questioned somehow, by attributing to the adipocyte a major immuno-modulatory role in the organism [36]. Immune function has been long time considered a quite distinct issue respect to bio-energetics, taking it aside from the metabolic and endocrine commitment with which the adipose tissue should be really engaged. Yet, a huge deal of reports
has recently moved the spotlight on the adipocyte as a leading actor in the complex immune-tissues cross talk [37-40]. Despite this, current research did not yet distinguished any purported existence of an exclusive adipocyte-immune cell from the common adipocyte collecting fats in the white adipose tissue (WAT) [36]. On the contrary, the scientific community attributed to the mature adipocyte in WAT the ability to modulate the immune function alongside its main task of lipid storage [41-43]. This allows the adipocyte to be described as having a sort of “secret” double life. Therefore, besides its endocrine role in fat storage, the adipocyte would be an immune-like cell *tout court*, inasmuch the adipose tissue was recently considered a tertiary lymphoid organ [44]. Obviously, this raises many interesting questions about the actual role of the adipose tissue in cancer pathogenesis and development [1,45].

So, is the adipocyte a multi-task cell?

 Actually, WAT was reported to home both regulatory T cells (Tregs) and group 2 innate lymphoid cells (ILC2s), keeping the immune function in the tissues under check, a role tuned by IL-33 from the stromal vascular fraction (SVF) [46]. A very recent paper actually showed that lineage negative (lin) SVF cells, which express the platelet-derived growth factor receptor alpha (PDGFR-α) and Sca-1, whereas they lack of the endothelial, hematopoietic and erythroid cell markers CD31, CD45, and Ter111, are active producers of IL-33 [46]. These cells showed typical genotypic features associated with adipose stem and progenitor cells, as expressing CD34, Itgbl1 (CD29), Ly6a (Sca-1), Pdpd, and Pdgfra genes [46]. Although IL-33 has been so far considered a master tuner of innate immunity, its very recent role is to maintain WAT homeostasis [47]. This cytokine is particularly intriguing, as it has been recently related with nutrition, due to the observation that IL-33 regulates the inflammatory process during obesity [48]. Therefore, we are discovering that the adipocyte is not only a fundamental player for the immune homeostasis in WAT but even that immune mediators serve as tuners of the adipose tissue turnover. Conversely, typical adipocyte products, such as lipid droplets, act as immune modulators [49].

A complex immune-adipocyte-tissue plasticity network has inflated the current debate on fat biology also in further men’ health concern, such as aesthetic surgery. This still raises these questions which role the adipocyte is fundamentally committed to, an immune or a plastic one? Or both? Or have we to turn our attention to a “third” option? Probably, the adipocyte might be considered a sort of sentinel of the “bodily self”, by checking and tuning the correct balance of different tissue types and their dynamics alongside the immune system [50-52].

So, the linkage with stem functions would suggest that the interplay between the adipose tissue and immunity should have a more demanding role than the simple check of a healthy metabolic homeostasis. An immuno-modulatory role, *via* a paracrine pathway, has been very recently recognized to mesenchymal stem cells (MSCs) [53-55], particularly close to the adipocyte biology, so suggesting that the adipocyte might lay at the crossroad immunity/stem-tissue homeostasis, so even suggesting for immunity a wider role within the classical well known immune self. In this perspective, the adipocyte tells of itself as a highly complex cell, finely tuning fundamental and strategic functions in the maintenance of tissue homeostasis, behaving in a much more intriguing way than expected and standing quite far from the sole acknowledged role of a lipid-tank collector. Actually, the very recent reports regarding the adipocyte, would suggest for a new outstanding activity in the “strange” life of the adipocyte, *i.e.*, the adipocyte as a master tuner of tissue homeostasis, not merely a regulator of a more general metabolic steady state. This feature may have important consequences on the comprehension of cancer development.

An intriguing functional kinship with MSCs of hematopoietic origin, sharing apparently a common role in maintaining the biological self *via* immunity, might shed light on the unusual and attractive “existence” of the adipocyte and on the real role of the adipose tissue, which may be of the utmost importance in tissue plasticity [56-58]. The adipocyte life cycle itself should give us insightful clues about the complex activity exerted by the adipose tissue in this perspective.

The first conundrum we should address is whether the white mature adipocyte is a commonly stable, differentiated cell or exhibiting a certain marked tuning ability in its adipose lifecycle. The most widespread view of the differentiated adipocyte is that it is the resulting outcome of the adipogetic pathway of mesenchymal precursors, usually collectively known as pre-adipocytes. The term pre-adipocytes may be yet outdated, as panoply of adipocyte precursors, called adipocyte progenitor cells (APCs), participate indeed in
the tissue/stem cell homeostasis, which is ultimately ruled by the adipose tissue, as previously suggested [59-62]. The master tuner of pre-adipocyte maturation into adult adipocytes is peroxisome proliferator-activated receptor gamma (PPAR-γ), but further agonists and modulators have been reported to be involved in this mechanism [63,64]. The APC population is formed by cells of mesenchymal origin (MSCs), fibroblast-like cells and a heterogeneous population of cells in the SVF [60,61] of the adipose tissue. Many APCs can be easily identified and isolated [65]. Most of the current research on the adipocyte lifecycle has been carried out on laboratory animals, such as mice or rats. In mice, WAT precursors were identified as PDGFR-α+ cells with the phenotype CD24+, but also the CD24- stem precursors Lin-CD29-CD34+Sca-1-CD24- were identified in the APC population, so suggesting that CD24- cells would generate CD24+ cells in vivo. CD24 negative cells will express late markers of the adipogenic process, i.e., behaving as pre-adipocytes [62]. The loss of CD24 marker may commit APCs to the further adipocyte development [62].

This perspective may shed light on the modulatory role of the adipocyte in tissue homeostasis, encompassing many further issues of men’s health, i.e., aging and cancer pathogenesis.

SVF precursors express CD34 (as stem cells) and CD29, whereas did not express peculiar markers of endothelium or hematopoietic lineage, such as CD31, CD45, and Ter111 [62]. Recent reports showed that in mice at least four subgroups of APCs in SVF can be identified on the basis of the expression of CD29 and CD34 but more than half of this population express the stem cell antigen 1 (Sca-1), being Lin-CD29-CD34-Sca-1-CD24- were identified in the APC population, so suggesting that CD24- cells would generate CD24+ cells in vivo. CD24 negative cells will express late markers of the adipogenic process, i.e., behaving as pre-adipocytes [62]. The loss of CD24 marker may commit APCs to the further adipocyte development [62].

This mechanism makes the adipocyte as a functionally “metastable” cell, in the sense that its stability is not of morphological type by of dynamical one [69].

Furthermore, post-adipocytes have been described in past reports [70] but recently restyled as a mature adipocyte able to resist the massive damage and stress, causing lipid loss, which usually occurs also during lipoaspiration procedures and fat grafting, and to rebuild functional fat cells [67]. Therefore the post-adipocyte is all but a terminal, out of service adipocyte. There might be, therefore, a close relationship between the mechanism of delipidation and the occurrence of post-adipocytes. Delipidated adipocytes suggested in the past the hypothesis that mature most-mitotic adipocytes may not be terminally differentiated, yet [71]. Delipidated adipocyte can give rise de novo to mature, fully functional adipocytes [72]. We still do not know if the shift from a post-adipocyte to a mature adipocyte crosses pathways including pre-adipocytes or adipocyte derived stem cells (ADSCs) as precursors of newly adipogenic cellular pools. To elucidate if post-adipocytes develop into mature adipocyte via an ADSC, this cell should express, for example, some specific phenotypic markers, such as CD90, CD44, CD29, CD105, CD13, CD34, CD73, CD166, CD10, CD49e, and CD59 and possibly be negative for markers, such as CD31, CD45, CD14, CD11b, CD19, CD56, and CD146 [73]. Further insights are needed to elucidate this issue.

Furthermore, delipidation may be a highly controlled physiological process, which can occur in ADSCs and leave adipocytes alive, neither undergoing apoptosis or autophagic mechanisms, nor dedifferentiation [74]. For
example, a controlled nano-induced *in situ* hyperthermia, causes adipocyte delipidation [74]. Interestingly, hypothermia inhibits bone-marrow derived MSCs and increases resistance to hypoxic stress by the SUMPoylation of fundamental proteins, such as PCNA, *oct-4, p53, and HIF-1*α [75]. This evidence suggests that delipidation may be a physiological mechanism of stress response. It is possible to speculate that delipidation caused by stress, may induce a population of ADSCs which over-expressing heat shock protein-70, enhancing the success and the efficacy of the autologous fat grafting in men’s aesthetic health [76]. Further research should address if this population of ADSCs may derive from the delipidation/post-adipocyte route (Fig. 1).

Finally, a dedifferentiation process of the mature adipocyte in WAT, can lead to adipose-derived stem cells

![Diagram](image-url)
(dedifferentiated adipose tissue, DFAT cells) with fibroblast-like phenotype [77]. There are controversial opinions about DFAT cells, i.e., if these fibroblast-like cells evolved from adipocytes and can reconstitute a new functional adipose tissue (practically post-adipocytes) or if they are true dedifferentiated adipocytes with stem potential [78]. The ambiguity is that fibroblast-like cells inducing new connective cell phenotype may be typical MSCs from the stem pool and not merely DFAT cells [78]. Anyway, this type of cells seem to emerge during a massive loosening of adipose tissue, when stress conditions should induce a fibrotic response [77,78].

**THE ROLE OF NUTRITION-DERIVED LIPIDS AND REACTIVE OXYGEN SPECIES**

Following the hypothesis suggested in Fig. 1, mature adipocyte in WAT looses lipids in response to stressors, such as ROS and enters a proactive rejuvenation, even passing via a stem phenotype. If confirmed, lipids should exert a fundamental signaling role in the mechanism described above about the adipocyte life cycle. Our idea is that adipocytes may “go back” to a relatively younger stage (delipided) and then, depending on the microenvironment conditions, turn again to a mature phenotype or even reaching a stem phenotype, which usually has an adipogenic commitment. This latest pathway should assure the adipose tissue to enhance its expansion potential. The balance adipocyte precursors/mature adipocytes is fundamental to warrant for a correct anatomical plasticity and tissue homeostasis, a condition that allows to consider the adipocyte a “quasi-stable” or metastable cell, though indicated as a post-mitotic, differentiated cell.

Nutrition has a leading role in this sense.

Recent evidence reported, for example, that dietary conjugated linoleic acid (CLA) reduces the fat burden in adipocytes, i.e., promoted the formation of delipided adipocytes. For example, trans-10 and cis-12 CLA but not cis-9 and trans-11 CLA, when added to stromal vascular cells in cell cultures containing newly differentiated human adipocytes, caused time-dependent dampening of the triglyceride content, insulin-stimulated glucose and fatty acid uptake. These same CLAs diminished also PPAR-γ and many PPAR-γ induced genes and increased leptin gene expression. The robust activation of the MEK/ERK signaling preceded changes in gene expression and caused the release of IL-6 and IL-8. Interestingly, the MEK/ERK activation by trans-10 and cis-12 CLA was inhibited by UO126 and pertussis toxin [79]. According to these authors, trans-10 and cis-12 CLA, delipided mature adipocytes by inducing the MEK/ERK signaling via an autocrine/paracrine action of adipocytokines, IL-6 and L-8 [79].

In would be particularly interesting to investigate if these lipids are spontaneously formed in vivo and, if yes, in which biochemical, physiological (or pathological) stage.

The role of the trans-10, cis-12 as antagonists of lipidic storage has been widely demonstrated in recent reports [80-83]. This CLA is therefore associated with caloric restriction, anti-obesity molecule, anti-lipid storage factor. Interestingly, this PUFA induces mature adipocyte delipidation [79]. The question is if these lipids are typical signaling mediators of the process in the adipocyte life cycle described before. While the isomer cis-9, trans-11 induces adipogenesis [84], it is possible to speculate on the existence of cell of “on/off switches” tuning the ratio t10,c12-CLA/c9,t11 CLA, as they play also a fundamental role in immunity [85]. We yet do not know if adipocytes may have enzymatic switching regulators (as a switch of two double C-C bonds, cis-trans, shifted of one position towards the ω6 end with reciprocal isomerization). At least 24 isomers of the 182, ω-6 linoleic acid were described [86]. Some studies have investigated the role of CLAs in adipocyte differentiation. The geometric isomer trans-10, cis-12 CLA reduces the number of pre-adipocytes [87] and inhibits glycerol-3-phosphate dehydrogenase, while cis-9 and trans-11 antagonized the other [87]. Furthermore, t10,c12 CLA inhibited the expression of PPAR-γ and of sterol regulatory element-binding protein-1c (SREBP-1c) [87] and did not affect the expression of CCAAT/enhancer binding protein alpha (C/EBP-α), therefore t10,c12 CLA cannot be considered a regulator of adipogenesis but of lipid storage and of the balance pre-adipocytes/mature adipocytes, i.e., of delipidation [87,88]. The isomer t10,c12 CLA may induce also inflammation [89]. Moreover, at least in porcine models, CLAs regulates adipogenesis in vascular stromal cells [90]. In these models, t10,c12-CLA inhibits adipogenesis in subcutaneous adipose tissue and promotes adipogenesis in intramuscular adipose tissue [91].

Usually, CLAs are obtained by an α9 desaturase. In adipocytes PUFAs are regulated by the fatty acid
desaturase FADS1 and FADS2 [91]. In adipocytes linoleic acid is the main tuner of FADS gene expression [91]. Therefore, it is tempting to speculate that CLAs are intrinsic regulators of the adipocyte “biomass” in sub-epidermal layers, where, in this perspective, it is conceivable that fibroblasts and keratinocytes may be fundamental sources of linoleic acid. Linoleic acid, in the presence of β-NADH, elicits a rapid and immediate ROS production in fibroblasts, which most probably act as signaling molecules to activate fibroblast oxidative burst [92].

It is also well known that ROS induce adipocyte differentiation via an increased expression of PPAR-γ and activating the CCAAT/enhancer-binding protein β (C/EBP-β) [93]. Anyway, this adipocyte differentiation occurs, at least in culture, if cells reach the confluence and under ROS oxidation. In this conditions, in the constant presence of inducing hormones, adipocytes activate PPAR-γ and differentiate into mature adipocytes and ROS enhanced cell phase S during the mitotic clonal expansion [93]. This is quite probably, the commonest, most orthodox circumstance regarding adiposity modulation in sub-epidermal fat tissues. Detached adipocytes are more likely to loss lipids and to enter a route of dedifferentiation, while adipocytes still present in a whole adipose tissue respond to the aforementioned cycle.

Conversely, ROS might activate also dedifferentiated adipocytes, most probably via a Notch/NADPH oxidase 4 interplay, but usually when ROS exceed a certain threshold, probably evaluated by mitochondria oscillation [94-96]. According to this hypothesis, there must exist a lipid signaling as a sort of “warning” signal, able to induce the adipocyte to shifting towards “younger” phenotypes and so enabling the adipose tissue to respond to the stressful stimulus maintaining the tissue homeostasis of the organism. Much ADSCs and dedifferentiated adipocytes might be therefore elicited when a defined “threshold”, probably induced by a certain milieu of soluble factors and cytokines, is overwhelmed, usually quite far from physiological conditions. Further research should yet elucidate this issue.

The role of ROS is therefore fundamental as a signaling pathway to set the adipocyte at the crossroad of the complex interplay energetic metabolism/tissue homeostasis. Therefore, they have a fundamental action also in the evolution of cancer, taking into account these issues.

The extreme plasticity of the adipocyte is a leading cause of many tumors, due to the occurring impairment in this complex cross talk [97].

In this perspective, the different type of adipose tissues in humans and the different types of fat composition in adipocytes, should exert a fundamental role in tissue homeostasis, so driving the complex signaling machinery preventing cancer in the organism.

Fats are therefore signaling molecules as well as ROS, a perspective that should raise the question if fats and ROS are more friends than foes for men’s health. A first interesting evidence is the role of lipids stored in cells as lipid droplets to counteract oxidative stress and move onward the metabolic-energetic machinery of cells [98]. Actually, lipid droplets are able to tune cell oxidative stress [99]. According to some authors, lipid droplets have the main property to buffer and modulate the delayed release of fats, both as signaling molecules and metabolic sources, and the delayed release is fundamental for many purposes, such as energy and redox homeostasis, tuning of autophagy [100] and of the ER stress [99]. In this sense, lipids actively participate as mediators in the cross talk between cells and tissues. Lipids in diet are therefore fundamental as possible elements in the creation of a complex signaling language among cells and within cells [101].

In this landscape, ROS may have also a fundamental task.

PPAR-γ and autophagy are intertwined in controlling both ROS signaling and lipid droplets production and turn over, having therefore a role in some type of cancer, such as colon cancer [102]. Actually, the role of PPAR-γ is more intriguing than expected, as it may tune the so called “two-compartment tumor metabolism” model, where a metabolic coupling has been suggested to occur between catabolic stromal cells and oxidative tumor cells [103]. In this models, cancers, for example breast cancer, is embedded in a complex microenvironment where a cross talk cancer cells/stromal cells occurs, in order to tune cancer survival. This cross talk involves also adipocytes. Cancer cells elicit in stromal cells glycolysis, lipid droplets, ROS formation from mitochondria and autophagy, while stromal cells activate a response with onco-metabolites that include fatty acids and peroxidized lipids [103].

Lipids modified by ROS and activated oxygen, are
powerful signal molecules even in plants [104].

For example, oxysterols are fundamental signaling molecules in cancer [105,106]. These molecules, occurring as cholesterol oxidized metabolites, may be produced by radical (ROS-dependent) mechanisms and make the so called oxysterone. They are fundamental actors in the tissue turnover, including cancer etiology, by interacting with a huge panoply of receptors, such as nuclear receptors (ROR, ERα, LXR) as well as protein G coupled receptors (CXCR2, SMO, EBl2, and so on) and becoming fundamental biomarkers in many chronic pathologies, including cancer, such as 4β-hydroxy-cholesterol or 7α-hydroxy-cholestenone [107].

The very recent awareness in science that lipids and their metabolites, together with lipid droplets, participate in the complex signaling language between tissues, so having a fundamental role in cancer, have put adipose tissue in a strategic focus, an intriguing perspective, particularly because adipocytes are able to develop stem features. Therefore, the new engagement in the biomedical research to highlight any aspects improving men’s health, is to take into consideration this fundamental issue.

CONCLUSIONS

This review would simply address some fundamental “hot topics” that deserve further attention and interest in science to attain a real improvement in our knowledge on men’s health and the onset of cancer. A huge deal of data regarding cancer and nutrition exists elsewhere but this manuscript aimed at stressing the major items able to drive further investigation towards this target, with a simple recommendation. Preventing diets from lipids at all, may not be a wise counselling to prevent chronic pathologies and cancer. Moderation is always advised but lipids are fundamental actors of our own health, as they can act as modulatory signaling molecules. Even ROS, in his perspective, may have a positive role in promoting health.

Therefore further research is needed to elucidate the complex role of ROS and adipose tissue in the different dietary habits engaged by humans.

Conflicts of Interest

The author has nothing to disclose.

Author Contribution

Conceptualization: SC. Data curation: SC. Formal analysis SC. Investigation: SC. Methodology: SC. Project administration: SC. Resources: SC. Software: SC. Supervision: SC. Validation: SC. Visualization: SC. Writing – original draft: SC. Writing – review & editing: SC.

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