The many secret lives of adipocytes: implications for diabetes

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Abstract

Adipose tissue remains a cryptic organ. The ubiquitous presence of adipocytes, the different fat pads in distinct anatomical locations, the many different types of fat, in each case with their distinct precursor populations, and the ability to interchange into other types of fat cells or even de-differentiate altogether, offers a staggering amount of complexity to the adipose tissue organ as a whole. Adipose tissue holds the key to improving our understanding of systemic metabolic homeostasis. As such, understanding adipose tissue physiology offers the basis for a mechanistic understanding of the pathophysiology of diabetes. This review presents some of the lesser known aspects of this fascinating tissue, which consistently still offers much opportunity for the discovery of novel targets for pharmacological intervention.

Keywords Adipokines · Adiponectin · Ceramides · De-differentiation · Exosomes · Fibrosis · Inflammation · Review · Sphingolipids · Vascularisation

Abbreviations

ECM Extracellular matrix
HIF Hypoxia-inducible factor
PET Positron emission tomography

Introduction

A large number of cell types and tissues serve as critical drivers for weight control within an organism. There are three basic pillars underpinning energy homeostasis. The first pillar comprises the tissues that contribute to energy homeostasis by controlling food intake, energy expenditure/metabolic rate and/or thermal regulation. The second pillar includes tissues that contain highly metabolically active cells, which contribute primarily in terms of energy consumption. The third pillar

consists of tissues that store energy in the form of triacylglycerols, carbohydrates or other metabolites. These three basic roles—regulation, consumption and storage—are obviously not strictly subdivided into individual tissues but, rather, every tissue contributes to some degree to all three processes. As such, there is certainly a high level of specialisation, and adipocytes are by far the most effective cell type when it comes to storing and, upon demand, releasing energy into the system.

While the storage aspect of adipocytes unquestionably remains central to systemic metabolic wellbeing, research over the past two decades has revealed a more nuanced picture of the adipocyte, much beyond its classical role as a cell type that simply esterifies NEFA, takes up glucose in the postprandial state and hydrolyses triacylglycerols under conditions of hypoinsulinaemia in the fasted state [1] (Fig. 1). Adipose tissue is an endocrine organ that releases protein factors, metabolites and signalling lipids, all of which are involved in an extensive network of inter-organ communication.

One of the critical questions that our laboratory has been addressing for several years now is: How do we maintain proper function of adipose tissue during obesity-induced expansion? That is, what are the critical determinants that allow adipose tissue to be metabolically ‘healthy’ vs ‘unhealthy’? This requires not only a proficient understanding of cellular and tissue physiology, but also hinges upon describing the terms metabolically ‘healthy’ and ‘unhealthy’. Although the precise definition of ‘healthy adipose tissue’ is still an issue of intense debate, what becomes apparent when analysing

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Fig. 1 The physiology of the adipocyte then and now. **(a)** The adipocyte was historically primarily known for its lipolytic action in the fasted state (low insulin), and its ability to esterify fatty acids and absorb glucose in the fed, high insulin state. **(b)** We now fully appreciate the complexity of the adipocyte as a source of a large number of different effector molecules. This figure is available as part of a [downloadable slideset](#)

different physiological states, from lipodystrophy to normal weight to obesity, is that metabolic health is not strictly a function of fat mass, and therefore different methods of assessment are needed. We should determine the health status of adipose tissue in the context of its epidemiological association with either the pathophysiological sequelae of obesity, or the ability of adipose tissue to maintain full ‘metabolic flexibility’ (i.e. the ability to adapt to feeding and fasting across the whole system, despite an elevated BMI). While the field continues to struggle with the exact definition of the term ‘adipose tissue functionality’, some key aspects of adipose tissue physiology are discussed below.

Adipose tissue is a complex organ

While the adipocyte dominates the field of energy metabolism as the protagonist of adipose tissue, there is more to a fat pad than the adipocyte. Adipose tissue requires proper delivery of essential nutrients and oxygen; therefore, optimal vascular function is critical. Vascular density can be genetically manipulated in rodents. Increasing vascular density stimulates adipose tissue to undergo healthy expansion [2]. The vascular

bed can also serve as an important source for mesenchymal stem cells, which are recruited to adipose tissue to become pre-adipocytes [3]. Upon demand, pre-adipocytes are activated to embark on a full adipogenic program [4]. Given that adipose tissue can change vastly in size, a tremendous challenge is imposed on its extracellular matrix (ECM), which must constantly adapt to the large alterations in volume [5]. Immune cells also play a major role in this process [6]. In particular, macrophages serve as a critical source for new ECM components and importantly, as modifiers of ECM constituents during adipose tissue remodelling [7]. Macrophages that lean towards an ‘M2’ phenotype are frequently considered to contribute to this process in a positive manner [8]. Traditionally, the proinflammatory cell population is referred to as ‘M1’ macrophages, and the remodelling cells as ‘M2’ macrophages. Even though these are very heterogeneous populations that fall into many additional subcategories, these functional definitions are still very useful [9]. Additional innate immune populations have been identified in adipose tissue, such as neutrophils, mast cells and eosinophils. Adaptive immune cells are also present, such as a variety of T cells and B cells [10]. The cellular composition and degree of infiltration of immune cells into fat tissue is in constant flux, depending on its metabolic status. There remain major gaps in our knowledge as to the precise role of each immune cell subtype in adipose tissue homeostasis. None of the immune cell populations that temporarily reside within adipose tissue express unique markers that distinguish them from the same populations in other tissues, or within the circulation. As these immune cells cannot genetically be manipulated selectively without affecting the same cells elsewhere in the system, the phenotypic analysis of immune cells specifically within adipose tissue is certainly complicated.

What goes wrong with adipose tissue expansion during obesity?

Many different phenomena can initiate the pathway to adipose tissue dysfunction. In our proposed model, we view adipose tissue expansion as a process that is critically dependent on adequate vascularisation. In rodent model systems, the degree of hypoxia in expanding fat pads is sufficient to initiate activation of hypoxia-inducible factors (HIFs) [11, 12]. Hypoxia is also observed in human adipose tissue, where fat expansion occurs at a slower rate than in rodents, although oxygen concentrations in humans may not be sufficiently low to cause widespread induction of HIFs [13]. Nevertheless, there is an increase in ECM constituents in both rodents and humans, which ultimately leads to fibrotic adipose tissue [14]. At least in murine models, it has been shown that the upregulation in the fibrotic program is driven by HIF1 α . As such, HIF inhibitors can be utilised to reduce local fibrosis to improve the

metabolic phenotype during obesity [15]. Numerous clinical studies draw correlations between enhanced adipose tissue fibrosis and a metabolically unhealthy phenotype. Fibrosis itself is reduced following weight loss, which includes bariatric surgery. Fibrosis is at least partially reversible, even though the process of reversal takes several months [16]. What becomes apparent when analysing different physiological states, from lipodystrophy to normal weight to obesity, is that metabolic health is not strictly a function of fat mass. In the lipodystrophic state, the lack of an appropriate storage compartment for triacylglycerols leads to severe insulin resistance as a result of ‘lipotoxicity’ [17]. In contrast, when examining the other end of the spectrum, a significant percentage of overweight, obese, and highly obese individuals, display normal metabolic variables [18]. This highlights the notion that it is primarily the *quality* of adipose tissue, and not the *quantity*, which serves as the key determinant of metabolic health [19, 20]. However, this should not be construed as an endorsement for obesity, as, from an epidemiological standpoint, increased fat mass is strongly correlated with insulin resistance, and even those individuals that display normal metabolic variables despite an increase in BMI, will exhibit a higher risk of developing diabetes as they age. Nevertheless, our laboratory and others have successfully developed murine models that allow us to effectively study these different metabolic states; from congenital lipodystrophy [21], inducible lipodystrophy [22], to obese and ‘massively obese yet metabolically healthy’ phenotypes [19, 23]. As such, these models should allow us to better define the exact characteristics of healthy adipose tissue [24]. Taken together, the hallmarks of healthy adipose tissue are as follows: (1) a high degree of vascular density within the fat depot; (2) minimal hypoxia and fibrosis; and (3) a low level of ‘M1’ macrophage infiltration into adipose tissue and a relatively low level of inflammation [19].

Apples vs pears: is it more complicated than that?

The conventional notions regarding fat distribution, which have been widely accepted for decades, still hold true. A fat distribution that leans towards a more central visceral location (i.e. the ‘apple’ shape), is epidemiologically associated with a less favourable metabolic phenotype. Conversely, a distribution where the subcutaneous fat depot is preferentially expanded, particularly in the lower extremities (i.e. the ‘pear’ shape), is typically associated with a more favourable metabolic phenotype. In addition to this, lower limb perigluteal adipose tissue mass displays a positive correlation with insulin sensitivity [25, 26]. While the global distribution of fat mass has garnered much attention, there are dozens of recently identified additional fat pads that are much less appreciated. While conventional methods entail visualising these fat pads through

anatomical dissection, more recent methods allow for the visualisation of highly metabolically active tissues by positron emission tomography (PET) scanning, and the latter is now applied in the clinic [27]. As such, the technique was initially employed to look at tumours but closer analysis of scans revealed an apparent seasonal increase in the ‘noise’ of tissues that avidly take up labelled glucose that was unrelated to any tumour lesion. These tissues consistently and very reproducibly ‘light up’ in PET images in specific anatomical locations, e.g. prominently in the subclavicular regions and along the spine. However, given their distribution, these depots are extremely difficult to study in humans. As such, rodent model systems do not seem to be particularly useful in this case, as the basic fat depot distribution appears to be rather different. However, our laboratory recently took advantage of a similar PET-based detection technique that utilises labelled glucose or lipids. This high-precision imaging system allowed us to effectively detect numerous additional fat pads in mice. These newly identified murine fat pads display a comparable distribution that effectively mimics the fat pad distribution in humans [28]. More importantly, based on studies of cold induction, histological examination and gene expression analyses, our laboratory showed that these novel fat pads display unique characteristics that allow them to be sub-characterised into classical white, beige/brite, or classical brown adipocyte categories (Fig. 2). The ultimate goal is to identify unique markers for these fat pads that will permit us to manipulate them selectively in order to study the function of these specific pads, systemically as well as within their local microenvironment.

More flexibility in fat cell ‘fates’ than ever anticipated

There are several subtle differences between different fat cells that the field is just beginning to appreciate. Beyond identifying the existence of classical white, beige and brown adipocytes, these subsets of adipocytes have the capacity to seemingly interchange between themselves. The subcutaneous white fat pad can effectively recruit beige fat cells in response to cold and/or β_3 -adrenergic receptor agonist stimulation. However, the visceral white fat depot is unable to do this, primarily because of the suppressive actions of the transcription factor known as zinc finger protein 423 (ZFP423) [29, 30]. Adding further to the complexity of the process, once a beige adipocyte evolves, it can essentially revert to a ‘dormant’ white adipocyte when mice are returned to room temperature [31].

It was traditionally believed that adipocytes are terminally differentiated cells that can undergo only three types of change: (1) an increase in size; (2) a decrease in size; or (3) undergo cell death, either by necrosis or apoptosis (Fig. 3). However, with the use of novel, highly effective labelling

Fig. 2 White, beige and brown adipocytes are morphologically and functionally very distinct and differ with respect to their mitochondrial content. There is a gradual decrease in lipid droplet size (unilocular in the white adipocyte, increasingly multilocular in the beige and brown adipocyte). This is in line with the primary role of the white adipocyte as a

storage compartment for lipids, whereas beige and brown adipocytes need extensive access to the lipid droplet surface to rapidly activate triacylglycerol and provide fuel for the much more abundant mitochondrial structures in these cells. This figure is available as part of a [downloadable slideset](#)

techniques, and with genetic tools that allow us to label all existing adipocytes to follow their fate, our laboratory recently identified a fourth type of change. There is now ample evidence that a fat cell can undergo ‘de-differentiation’ by reverting back to a pre-adipocyte, a fibroblast or a myofibroblast [32]. Our group recently reported that in the mammary gland, adipocytes undergo a full de-differentiation program during late pregnancy and lactation [33]. Upon involution of the mammary gland, i.e. cessation of lactation, milk-producing lobules undergo apoptosis, thus allowing the re-appearance of adipose tissue and the restoration of its initial architecture. The original adipocytes that de-differentiated

thus re-appear to fully reconstitute the adipocyte population in the entire mammary gland. Importantly, this is a process that repeats itself over multiple rounds of pregnancies, with the vast majority of the adipocyte population cycling between the differentiated state, and the undifferentiated precursor state. This highlights a remarkable level of plasticity for the mature adipocyte. Moreover, there is now ample indirect evidence that such events occur under other pathophysiological conditions. In particular, Varga and colleagues suggested that dermal adipocytes can de-differentiate into myofibroblasts over the course of dermal sclerosis [34]. Our own unpublished observations (P. E. Scherer) suggest a recurring de- and re-

Fig. 3 De-differentiation and re-differentiation as part of the adipocyte life cycle. Adipocytes can either stay stagnant, grow in size, shrink or undergo apoptosis or necrosis. As an additional option, they can regress to an adipocyte precursor state, or become fibroblasts or highly fibrotic

myofibroblasts through a process called adipocyte (myo)fibroblast transition (AMT). The cells can undergo this cycle multiple times. This figure is available as part of a [downloadable slideset](#)

differentiation process in dermal adipocytes over the course of the hair cycle. Similarly, during invasion of transformed ductal epithelial cells into the stroma of a mammary gland, adipocytes are replaced by fibroblasts, which are most likely myofibroblasts derived from adipocytes that have undergone widespread lipolysis.

These observations raise the following important unanswered questions: Is the de-differentiation process part of the normal life cycle of any adipocyte, i.e. is this a stochastic process during which at any given time a small number of adipocytes de-differentiate? Specific physiological conditions, such as weight loss, may increase the percentage of cells that lean towards de-differentiation. Is this process even more prominent during times of extreme weight loss, such as cancer-induced cachexia? With the novel labelling techniques that are now widely available, these pressing questions can now be addressed in the near future.

The adipocyte as an endocrine cell

As mentioned in the Introduction, adipose tissue is an endocrine organ, and it releases vast amounts of secretory factors into the circulation for inter-organ communication [35]. Since adipose tissue can represent up to 50% of total body weight, it is thus considered a significant endocrine organ with profound system-wide effects. Early indications that adipocytes may communicate at a paracrine and endocrine level originated from the observation that they release $\text{TNF}\alpha$ [36] and a component of the complement system, adipsin [37]. Soon thereafter, leptin and adiponectin were cloned [38, 39], representing the first true adipokines identified, i.e. secretory factors whose expression is highly enriched in the adipocyte. Both leptin and adiponectin proceeded to be extensively studied over the decades, with tens of thousands of papers published on them, both as clinical biomarkers, in addition to in-depth mechanistic studies delineating their physiological role in metabolism. Several additional factors have been added to the list of adipocyte-derived secretory proteins over the years. These include numerous proinflammatory components, acute-phase reactants, ECM proteins and upstream factors that regulate ECM proteins [40]. Noteworthy members of the adipokine list also include resistin and endotrophin. Each adipokine could have an entire review article devoted to it. However, for the purpose of the discussion here, we will focus on a few selected adipokines.

Adiponectin, a highly versatile anti-lipotoxic agent

Adiponectin possesses numerous properties that render it an extremely unique anti-lipotoxic agent. Unlike other adipocyte-

derived factors, adiponectin tends to display an inverse correlation with obesity. The greater the fat mass, the less adiponectin there is in circulation [25]. Moreover, there are even stronger correlations between the functional integrity of adipose tissue and plasma levels of adiponectin. For example, even when adjusted for BMI, metabolically healthy individuals display higher levels of adiponectin compared with metabolically unhealthy individuals [41]. Thousands of studies have shown that plasma adiponectin levels are a direct reflection of metabolic fitness, with high adiponectin levels correlating with improved insulin sensitivity, reduced inflammation and enhanced survival of susceptible target cells, the latter primarily pancreatic beta cells and cardiomyocytes [42, 43].

Even the slightest elevation in adiponectin levels produces an extremely broad range of effects. The anti-inflammatory, insulin-sensitising and anti-apoptotic properties of adiponectin are consistent with a potential impact on the sphingolipid pathway. Elevated levels of ceramides are associated with insulin resistance, inflammation and apoptosis [44]. Specifically, ceramides are converted into sphingosines through a single enzymatic step, which, in turn, is highly associated with improved cellular survival and proliferative responses [45]. Experiments on transgenic animals with altered adiponectin levels demonstrate that enhanced adiponectin action profoundly reduces tissue and circulating levels of toxic ceramides, and therefore has a positive metabolic impact [45]. Indeed, *in vitro* and *in vivo* studies have shown that increasing the number of adiponectin receptors on cells greatly enhances ceramidase activity [46]. Furthermore, determination of the crystal structure of two purified adiponectin receptors revealed inherent ceramidase activity associated with the receptor [47, 48]. Thus, based on the available data, I believe that the majority of the effects that adiponectin exerts *in vivo* can be explained by an effective lowering of toxic ceramide species, which in turn leads to numerous secondary effects downstream, and/or an associated increase in sphingosine phosphate levels. Importantly, the adiponectin receptors are essential for these specific adiponectin-mediated improvements. Our group has also recently shown that the overexpression of adiponectin receptors in the liver, or in adipocytes, prompts a reduction in ceramide levels and a rapid improvement in insulin sensitivity that, ultimately, leads to a profound reduction in diet-induced hepatic steatosis [46]. These metabolic read-outs are effectively ‘pheno-copied’ through overexpression of a specific acid ceramidase within the same tissues [49].

Since the adiponectin receptors are essentially ubiquitously expressed, adiponectin can exert its beneficial effects in almost every cell type. Indeed, our group observed the potent effects of adiponectin in pancreatic beta cells, cardiomyocytes, hepatocytes and many other cell types [50]. More recently, the kidney has emerged as an interesting and unappreciated target of adiponectin action. As a representative example, our

laboratory studied the effects of genetically altered adiponectin levels on the POD-ATTAC model [51]. This is a mouse model in which inducible apoptosis selectively occurs in mature podocytes, which means that it effectively serves as a model for diabetic nephropathy. Upon provision of a partial apoptotic stimulus to the podocyte, we reported that, in the presence of transgene-induced higher levels of adiponectin, the regenerative and functional aspects of the kidney were greatly enhanced. In addition, adiponectin reduces fibrosis and enhances the generation and recruitment of new podocytes. Adiponectin has also been shown to exert critical effects on kidney mineral metabolism [51]. In fact, very similar observations can be made with an analogous model for pancreatic beta cells [52].

Combined, these observations have been instrumental in giving us a refined mechanistic understanding of the physiological actions of adiponectin. They have also brought the ceramide axis into focus as an important therapeutic area; whether it is at the level of ceramide degradation in the form of ceramidase activity, or in the form of an inhibitory effect on ceramide biosynthesis [53]. Several recent clinical publications make a firm case for the correlation between elevated ceramide levels and insulin resistance, mitochondrial dysfunction and inflammation (e.g. [54]).

Several critical tools and methodologies have also emerged from the study of adiponectin. The adiponectin promoter has proved extremely useful for selectively driving transgenic gene expression in the adipocyte [55]. This allowed us to generate an inducible gain- or loss-of-function mouse model, by taking advantage of *tet* (doxycycline)-inducible promoters that can be directed towards the fat cell [55]. This enabled us to proceed with the inducible loss of adiponectin in the adult mouse [56]. The key advantages of these novel murine models were immediately apparent, as we were able to study the physiological consequences of an *acute* loss of adiponectin. As expected, basic physiological characterisation of the mice with immediate loss of adiponectin revealed a more severe phenotype than that observed for the congenital loss of adiponectin. Namely, severe insulin resistance (as determined by euglycaemic clamp experiments), profound transcriptional alterations (including a significant downregulation in *Ppar γ* expression levels), enhanced local inflammation and increased levels of several ceramide species. Importantly, critical experiments such as these helped to unravel some of the additional and essential aspects of adiponectin function. Upon elimination of adiponectin, mice no longer tolerated insulinopaenia. More specifically, upon streptozotocin treatment, mice lacking adiponectin developed severe hypertriglyceridaemia, and this is even worse in an inducible loss-of-function setting as it ultimately yields a lethal phenotype. Future studies are needed to delineate the impact of the inducible loss of other key adipokines, such as the loss of leptin in the adult mouse, with or without the loss of adiponectin.

Additional means of communication between tissues

With intense exchange of metabolites, lipids and protein factors, the complexity of trafficking between plasma and the adipocyte is frequently underestimated. Plasma components must cross a tight endothelial barrier and travel through the stroma to reach the adipocyte, and the same is true in terms of the release of components from the adipocyte into the plasma. While there is clear evidence that metabolites travel through the conventional diffusion process, over the past year several studies have emerged that reveal strong evidence for additional mechanisms of transport, including ‘exosomes’. Trafficking of exosomes has been extensively studied in the area of oncology; however, there is increasing evidence that these vesicular structures play an important role in metabolism, particularly as trafficking intermediates for adipose tissue. Mice lacking the microRNA processing enzyme *Dicer* specifically in adipocytes, exhibit a substantial reduction in circulating exosomal microRNAs [57]. Furthermore, adipose tissue macrophage-derived exosomes also contain vast amounts of microRNAs, which can travel to other tissues to alter insulin sensitivity [58]. Recent data from our laboratory suggest extensive exchange of exosomes between the endothelium and the adipocyte [59]. In fact, there is a high degree of exchange of plasma membrane subdomains between the two cell types (primarily materials that include raft structures containing caveolins) (Fig. 4). Sphingolipids, and several other protein components are also transported through this mechanism, with the degree of trafficking highly dependent upon the nutritional status of the organism. This increased appreciation for exosomal-based trafficking as a means for inter-organ communication thus opens up an entirely new and exciting area of research. Given there is such an extensive exchange of components between different cell types, existing data should be re-visited and re-evaluated in the context of exosomal trafficking.

The adipocyte as a drug target: does it still have anything new to offer?

In light of the phenomena listed above, our laboratory recently embarked on a comprehensive investigation of the potential of the adipocyte as a drug target [53]. Given the central role the adipocyte plays in systemic metabolic homeostasis, as well as the multifaceted aspects of the many different fat pads with their paracrine and endocrine functions, adipose tissue remains one of the most promising options for target discovery in the areas of metabolism and obesity. In terms of our understanding, we have only just scratched the surface of this complex cell type, and with the development of increasingly sophisticated ways of genetically modifying adipocytes, more aspects will surely be revealed. I believe the adipocyte will

Fig. 4 Adipose tissue trafficking critically depends on exosomes as vehicles across the interstitial space. These exosomes are likely to have distinct cargo, depending on the exosomal origin. Macrophage-derived exosomes have established populations of microRNAs, whereas the adipocyte-derived exosomes have been characterised for their vast amounts of sphingolipids, the protein scaffold caveolin and a number of mitochondrial constituents. This figure is available as part of a [downloadable slideset](#)

still give rise to a number of novel protein therapeutics as well as specific targets for small molecule inhibitors with potent anti-diabetic effects.

Many questions remain

Naturally, this review has primarily focused on the metabolic aspects of adipose tissue. However, many additional questions remain. Several pathological features of adipose tissue have yet to be explained mechanistically. Lipoedema is a key example. Lipoedema is the pathological expansion of adipose tissue in highly selective areas, primarily in the lower extremities, with fat accumulation evident in a column-like shape in the legs and buttocks [60, 61]. Predominantly affecting women, lipoedema is observed in up to 10% of females, and can be often misdiagnosed as obesity. At the later stages of the

condition, lipoedema can spread to the upper extremities to cause lymphoedema. Despite the large number of individuals affected, proper diagnostic criteria and a basic mechanistic understanding of what causes the clinical manifestation of the disease are lacking. Several additional diseases, such as Dercum's disease and lipomatosis, also involve pathophysiological changes of adipose tissue with underlying mechanisms we have yet to understand [62]. Less pathological and more cosmetic, are issues related to wrinkle formation (which we could consider as local lipodystrophies), as well as cellulite formation. There is ample interest and large demand to better understand the mechanistic basis of these age-related changes.

Other aspects of adipose tissue physiology (Fig. 5) relate to infectious disease and cancer. Adipocytes are prime targets for a number of parasites, including the causative agent of Chagas' Disease, *Trypanosoma cruzi*. The *Trypanosoma cruzi* parasite infects adipocytes, taking advantage of their long

Fig. 5 The adipocyte has a metabolic impact on many different tissues (shown in black text). The fat cell is also a primary target for a number of infectious entities, including trypanosomes (shown in the micrographs), which target adipocytes because of their longevity (providing protection from the immune system). Furthermore, there is an intense local and systemic crosstalk between adipocytes and growing tumour lesions, and mediators of this crosstalk are shown in red text. This figure is available as part of a [downloadable slideset](#)

half-life (up to 10 years in humans). In these cells, they remain undetected by the immune system, and not only contribute to the cardiomyopathy associated with the chronic stage of the disease, but also inflict extensive damage locally within adipose tissue itself [63].

Lastly, the still somewhat mysterious connection between increased BMI and cancer incidence has only partially been unravelled, particularly for a subset of cancers, which include endometrial cancers, post-menopausal breast cancers, pancreatic cancers and colon cancers. While we appreciate how tumour cells and adipocytes influence each other's metabolic programs, the field still needs to identify the key culprits that mediate the increased susceptibility for tumour initiation [64].

A final thought

To date, with so many different shades of fat identified, and a myriad of systemic alterations associated with dysfunctional adipose tissue, we hope there is still plenty of room to attract new talent to these research areas. Many unresolved issues await targeted research, with clinicians and basic scientists working hand in hand to identify novel means by which our adipose tissue can be reprogrammed into being the benign protective bystander that it was originally meant to be, before we provided massive insults to the tissue through excess energy intake.

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