Genomic and epigenomic regulation of adipose tissue inflammation in obesity

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Chronic inflammation of adipose tissue is viewed as a hallmark of obesity and contributes to the development of type 2 diabetes and cardiovascular disease. According to current models, nutrient excess causes metabolic and structural changes in adipocytes, which initiate transcriptional programs leading to the expression of inflammatory molecules and the subsequent recruitment of immune cells. Recent advances in deciphering the underlying mechanisms revealed that key regulatory events occur at the genomic and epigenomic levels. Here we review these advances because they offer a better understanding of the mechanisms behind the complex obesogenic program in adipose tissue, and because they may help in defining new therapeutic strategies that prevent, restrict, and resolve inflammation in the context of obesity.

Adipose tissue inflammation: a hallmark of obesity

Worldwide changes in lifestyle have caused a global obesity epidemic, with an estimate of over 700 million affected people in 2015. Accordingly, health authorities including the World Health Organization (WHO) and the American Medical Association (AMA) promote the designation of obesity as a new ‘disease’. However, the absence of a single, clear, authoritative, and widely accepted definition of obesity, a concern to both clinicians and obese patients, emphasizes the multifactorial and sometimes poorly understood nature of the disorder [1].

Traditionally, obesity has been viewed as the result of an imbalance between energy intake and expenditure, driven by increased consumption of food with high caloric content and a sedentary lifestyle. Interindividual differences have been often ascribed to genetic variations in genes related to energy metabolism. Indeed, many genetic and epidemiological studies in the 1980s on cohorts of twins and adopted children revealed a statistically significant contribution of genetics to the development of obesity [2,3]. Although these

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approaches led to the identification of some causal genes in monogenic disease (that are usually severe with early onset), the approach was less fruitful in identifying causal genes in common forms of obesity [4–7]. In recent years obesity and its related complications have also been associated with other factors such as sleep, gut flora, or nutrients, which might increase susceptibility to weight-gain and obesity-related complications through epigenetic changes (see Glossary) (Figure 1) [8–10].

Experimental and epidemiological evidence has linked obesity and related metabolic complication to chronic inflammation. In fact, it is suggested that chronic inflammation in the context of metabolic disorders (termed ‘metaflammation’) might be the result, at least in part, of epigenetic alterations. Adipose tissue inflammation, a hallmark of obesity (Box 1), is present to different degrees in different individuals, and might be the consequence of epigenetic alterations in response to lifestyle and other environmental factors that influence chromatin

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**Figure 1.** Components of epigenomic responses that influence adipose tissue inflammation in obesity. Environmental factors, lifestyle, and genetic makeup result in ‘personalized’ epigenomic responses and alterations in metabolic pathways, and these are likely to influence adipose tissue metaflammation during the progression of obesity. Highlighted are the major components which influence the propagation of such ‘metaflammatory epigenomes’ in adipose tissue.
Box 1. Inflammatory events in obesity

Dietary manipulation of rodent models has shown that both high-fat diet (HFD) or high-caloric diet (HCD) feeding induce short-term acute inflammation in adipose tissue. This phase is termed the early phase of the inflammatory response and does not involve immune cells [13]. The way in which this inflammation is initiated remains unclear. Storage of excess nutrients in the adipose tissue result in hypertrophic adipocytes, lipid dysregulation (accumulation of diacylglycerol and ceramide), mitochondrial dysfunction (oxidative stress), and endoplasmic reticulum stress [91,92]. Activation of inflammatory cascades and an increased secretion of inflammatory mediators is also observed (Figure 2) that attract immune cells such as M1 polarized (proinflammatory) macrophages [23]. This phenomenon is termed chemotaxis. Indeed, M1 macrophages are enriched within the adipose tissue in obesity, thereby orchestrating an adaptive immune response [93]. Lymphocytes have also been recently discovered to infiltrate human adipose tissue. Polarization of lymphocytes is dependent on the inflammatory environment and the capacity of adipose tissue cells to present antigens [94]. The initial idea that macrophages are responsible for T cell activation was challenged by recent evidence showing that adipocytes can also activate T cells [95]. All these inflammatory processes contribute to the development and maintenance of adipose tissue inflammation in obesity. The phenotype of immune cells and adipocytes in obesity might be triggered through specific transcriptional circuits in response to both genomic (alterations of transcription factor binding and function) and epigenomic (alterations of chromatin modifications) regulatory events.

Recent progress in dissectioning transcriptional alterations in gene networks, that are specifically linked to adipose tissue inflammation in obesity, highlight the importance of a tight coordination of such networks for appropriate gene expression for a healthy state. These alterations include activation and promoter binding of specific transcription factors, referred to as genomic regulators, the recruitment of chromatin modifying coregulators, and the induction of non-coding RNAs referred to as epigenomic regulators (Figure 1).

Here we review current insights into the genomic and epigenomic regulation of adipose tissue inflammation, which offer a better understanding of the complex obeseogenic program and may help in defining new therapeutic strategies to prevent, restrict, and/or resolve inflammation in the context of obesity.

Genomic regulation

Transcription factors involved in adipose tissue inflammation in obesity

Activation of innate immunity pathways. A crucial finding linking inflammation and adipose tissue dysfunction was the observation that the Toll-like receptors (TLRs), a family of pattern-recognition receptors that play a crucial role in innate immunity, respond to dietary fatty acids. Specifically, saturated free fatty acids (FFAs) induce adipose tissue inflammation through activation of the TLR4 pathway [11]. Mice lacking TLR4 are protected against high-fat diet-induced obesity, inflammation, and insulin resistance because they are resistant to the suppression of insulin signaling during lipid infusion, and exhibit reduced insulin-mediated changes in systemic glucose metabolism [12]. TLRs as well as the tumor necrosis factor α (TNFα) receptor (TNF-R) typically activate a broad spectrum of proinflammatory markers including cytokines and transcription factors such as nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), its inhibitor IKKβ, and Jun N-terminal kinases (JNKs) [13] (Figure 2). Inhibition of IKKβ or JNK by synthetic inhibitors or their genetic deletion prevents adipose tissue inflammation and resolves obesity-induced insulin resistance, highlighting their key functions in adipose tissue inflammation [13] (Figure 2). Interestingly, JNK depletion in macrophages reduces tissue infiltration by macrophages (known as adipose tissue-associated macrophages – ATMs), and blocks the induction of inflammatory gene expression in adipose tissue [14] (Figure 2).

In addition to ATMs, several other immune cell types are found in the obese adipose tissue. Inflamed adipose tissue is enriched in T lymphocytes, which under conditions of obesity promote an increase in the levels of interferon γ (IFNγ). IFNγ plays a crucial role in the regulation of adipose tissue inflammation and enhances the production of various inflammatory cytokines, including TNFα [15,16]. The increased IFNγ levels result also in the activation of interferon regulatory factors (IRFs), another class of transcription factors involved in adipose tissue inflammation (Figure 2). Indeed, IRF-1, -3, -4, -7, and -9 have all been reported to regulate adipogenesis and ATM polarization [17–19]. Interestingly, IRFs have dual functions because they not only activate but also repress transcription. In particular, IRF4 and IRF7 appear to repress anti-inflammatory genes in adipocytes [20,21], thus propagating the inflammatory state. Although the underlying mechanism of repression remains unclear, the involvement of specific corepressors and a distinct epigenomic landscape specifying the repressive chromatin environment is likely to be one contributing factor (discussed below).

Nuclear receptors and adipose tissue inflammation. Although the activation of proinflammatory transcription factors is a prerequisite for adipose tissue inflammation, the concomitant suppression of anti-inflammatory transcription factors and their coregulators is also part of the equation. An example is found within the nuclear receptor family, where various nutrient-sensing members are known for their potent anti-inflammatory activities [22,23]. Peroxisome proliferator-activated receptor γ (PPARγ), a key regulator of adipogenesis and the genomic target for the anti-diabetic drugs thiazolidinediones (TZDs) [24–27], has anti-inflammatory action, although its expression is reduced in inflamed adipose tissue [28]. Several possible mechanisms may account for the anti-inflammatory action of PPARγ in the context of obese adipose tissue. For example, because PPARγ activation by TZDs improves insulin sensitivity, partially through promoting fatty acid storage as triglycerides in adipocytes, it reduces lipotoxicity and counteracts inflammation in adipose tissue [29]. Indeed, diabetic patients treated with TZDs show improvement in their inflammatory parameters despite gaining weight [30].

Another mechanism might be a direct inhibition of proinflammatory transcription factors in adipose tissue
via transrepression, reminiscent of the anti-inflammatory action of PPARγ and liver X receptors (LXRs) in macrophages [31,32]. However, although the transrepression pathway has been validated in different macrophage populations, in the context of vascular inflammation and atherosclerosis and with additional nuclear receptors, [33], it has not yet been established in adipocytes (Figure 3) and warrants more investigation. More recent findings suggest that PPARγ may modulate inflammation by regulating the expression of anti-inflammatory transcription factors and their coregulators in adipocytes [29]. For example, the E-box transcription factor Twist-related protein 1 (TWIST1) controls in part the expression of two subunits of an anti-inflammatory complex that represses transcription, referred to as G protein pathway suppressor 2 (GPS2) and silencing mediator for retinoid and thyroid hormone receptor (SMRT) (described below in Box 2 and Figure 3) [34]. Interestingly, TWIST1 expression, which is also regulated by PPARγ, is reduced in obese adipocytes and correlates with the inflammatory status of the tissue [35,36]. Thus, the GPS2/SMRT corepressor complex could be a mediator of the anti-inflammatory action of PPARγ that specifically affects signals originating from the inflamed adipocytes.

In addition to its effects on macrophages and adipocytes, PPARγ may also control adipose tissue inflammation and insulin sensitivity by stimulating the accumulation and function of regulatory T cells (Treg) in visceral adipose tissue [27]. Finally, another class of transcription factors known as Krüppel-Like factors (KLFs) appear to be involved in the regulation of adipose tissue inflammation as well. As observed with PPARγ, reduced expression of KLF4 seems to be associated with elevated expression of proinflammatory markers [37].

Transcriptional coregulators
Epigenomic checkpoints of inflammatory gene expression
The term ‘coregulator’ describes a structurally and functionally diverse class of proteins and multiprotein complexes that do not bind directly to DNA but instead associate with DNA-bound transcription factors to regulate gene transcription (Figure 3). Coregulators can either activate (coactivators) or inhibit (corepressors) transcription through modifications of the chromatin structure. Importantly, many coregulators modulate transcription in a cell- or tissue-specific manner, thus creating an additional level of control, specificity, and complexity [31]. Although
in vitro and cell-based studies have provided great insights into the structure and function of many coregulators and their complexes, their in vivo function and transcription factor specificity remain poorly understood partly because most of the full-body coregulator knockout mouse models are embryonic lethal [38]. Clearly, tissue-specific knockout models are required to study coregulator function in vivo and recent studies that have taken on this task have revealed novel functions of some coregulators in adipose tissue.

Coactivators that drive inflammation. Inflammatory transcription factors such as NF-κB, AP-1, and IRFs are dependent on coactivators. The coactivators CREB-binding protein/p300 (CBP/P300) and switching-defective sucrase non-fermenting (SWI-SNF) activate transcription of these inflammatory genes by increasing histone acetylation of their promoters (Figure 3) [39,40]. NF-κB interacts with CBP/P300 and SWI-SNF to induce transcription of its target genes such as TNFα and interleukin 6 (IL-6) [41,42], thus propagating the inflammatory profile. Receptor interacting protein 140 (RIP-140, NRIP1), originally described as a nuclear receptor coactivator, can also act as a coactivator to promote the expression of proinflammatory genes [43]. RIP140 is recruited to the promoters of NF-κB target genes and stimulates transcription by stabilizing the formation of the trimeric RelA and CBP/P300 complexes. GPS2 (G protein pathway suppressor 2), a subunit of the NCOR (nuclear receptor coactivator)/SMRT corepressor complex, can independently act as a coactivator by directly interacting with several nuclear receptors including the oxysterol receptor LXR [44]. Most often this regulation appears to be promoter-specific, raising the question of what determines context selectivity. Different chromatin structures and binding site compositions, distinct promoter-bound transcription factor sets, and/or the contribution of post-translational modifications might be such determinants.
Box 2. GPS2, an emerging anti-inflammatory player in human obesity

G protein pathway suppressor 2 (GPS2, also known as AMF-1) is a small protein initially discovered in yeast for its capacity to inhibit lethal G protein subunit-activating mutations in the pheromone response pathway. The first evidence that GPS2 acts as anti-inflammatory protein stems from experiments in yeast and mammalian cells where it was described to interfere with JNK1 activation. Subsequently, GPS2 was identified as a core subunit of NCoR/SMRT/HDAC3 corepressor complex, also supported by recent structural data [96]. Several lines of evidence suggest an important role of GPS2 in the control of transcription in inflammation. GPS2 acts as an anchor of SUMOylated nuclear receptors, such as LXRα or liver receptor homolog-1 (LRH1), with the NCoR/HDAC3 corepressor complex, allowing transrepression of inflammatory gene expression in hepatocytes. In the absence of GPS2, the NCoR complex is cleared from promoters, thus favoring transcription of inflammatory genes. Moreover, two recent studies have revealed genomic and non-genomic functions of GPS2 in adipocytes. Evidence provided by Perissi and coworkers suggests that GPS2 functions as a dual inhibitor of TNF-R signaling both in the cytoplasm and in the nucleus [50]. Also, transgenic overexpression of GPS2 in mouse adipocytes triggers insulin resistance. Moreover, the GPS2/SMRT corepressor complex is dysregulated and associated with inflammatory markers (IL-6) in adipose tissue of human obese subjects [34]. This dysregulation promotes derepression of inflammatory gene transcription, and this is reversed when GPS2 is overexpressed in obese adipocytes. These complementary studies establish that GPS2 acts as a repressive checkpoint in the regulation of inflammation in mouse and human adipocytes. In addition to its repressive activity, GPS2 may favor gene transcription at specific loci by behaving as a coactivator, as demonstrated for resistin in mouse adipocytes [50]. The next challenging step will be to understand how the transcriptional and non-transcriptional facets of GPS2 action regulate inflammatory responses not only in adipocytes but also in adipose tissue immune cells.

Corepressors that block inflammation. In recent years it has become clear that corepressors interact with inflammatory transcription factors to prevent their activation, thereby putting a molecular brake on inflammation (Figure 3). During proinflammatory signaling, corepressor complexes are cleared from promoters and replaced by coactivators to induce gene transcription. This transcriptional event is usually termed the ‘derepression pathway’ [32,45] (Figure 3). The corepressors NCoR and SMRT have emerged as important regulators of inflammatory gene transcription [46]. They assemble multiprotein complexes containing histone deacetylases (HDACs) and potentially other activities which block transcription, and clearance of NCoR and/or SMRT from inflammatory promoters is necessary to activate the transcriptional machinery. NCoR has been described as the main corepressor of inflammation in hepatocytes and macrophages [33,47]. Indeed, macrophage depletion of NCoR derepresses the main inflammatory genes controlled by NF-κB, AP-1, and Ets [48]. Although both NCoR and SMRT are corecruited to chromatin regions and participate in the regulation of inflammatory genes [49], less is known about the specific role of SMRT in the regulation of inflammatory genes in macrophages.

Recent studies have further refined these initial findings and identified new pathways highlighting the in vivo specificity and functional diversity of corepressor action. Although specific depletion of NCoR in adipocytes promotes adiposity [34,50], an effect mainly attributed to the hyper-activation of PPARγ, the increase of weight gain is not corroborated with inflamed adipose tissue. In addition, macrophage infiltration in adipose tissue was lower in NCoR knockout mice and was associated with decreased expression of TNFα and IL-1β. In agreement, another study demonstrated that NCoR is not dysregulated in adipose tissue or adipocytes of obese subjects, nor is it involved directly in the control of inflammatory gene transcription [34]. In contrast to what was observed in macrophages and liver, SMRT seems to be involved in the regulation of adipose tissue inflammation. Indeed, SMRT mRNA and protein expression in human adipose tissue and adipocytes is decreased in obese subjects, and is inversely correlated with inflammatory gene expression. Unexpectedly, GPS2 is an important player in the transcriptional repression of inflammatory genes mediated by the SMRT complex [34,50]. GPS2 anti-inflammatory actions appear to be mediated by both genomic and non-genomic regulation (discussed in Box 3). More recently, another subunit of the NCoR/SMRT complex, termed TBL1 related protein 1 (TBLR1), was also found to be involved in the regulation in metainflammatory events in adipose tissue [51]. Adipocyte-specific TBLR1 knockout mice display aggravated adiposity and metabolic disturbances such as glucose intolerance and insulin resistance. In addition, correlation analysis in human obese subjects revealed a negative association between circulating levels of the inflammatory marker C-reactive protein (CRP) and the expression of TBLR1 mRNA in adipose tissue. Overall, these new findings are crucial because they assign a role for corepressor complexes in obesity-linked adipose tissue inflammation, which can be exploited for therapeutic intervention. Along these lines, the stabilization of corepressors at regulatory enhancers and promoters of inflammatory genes, in specific cells or tissues, might be an exciting strategy to block inflammatory gene expression. For example, many lipid-sensing nuclear receptors including PPARs and LXRα, all known for their anti-inflammatory actions, have the potential to antagonize the derepression pathway by stabilizing SMRT/NCoR complexes at regulatory chromatin regions and preventing their clearance upon proinflammatory signaling [32,33]. However, many details of these probably multiple trans-repression mechanisms remain to be clarified, such as the specific requirement of receptor SUMOylation [52] and the docking mechanism of receptors to the complex. Regarding the latter, subunits such as GPS2 and Coronin2A (Coro2A) have been proposed to be essential for receptor docking, which may involve specific recognition of modified receptors by different SUMO subtypes [33,53,54]. Although these corepressors are established repressive checkpoints of inflammatory gene expression, many questions remain to be addressed. Is derepression sufficient to initiate adipose tissue inflammation? What is the repertoire of genes regulated by these corepressors? And what ‘obesity’ signals dismiss corepressors from target genes?

Epigenetic modifications: is there an adipose tissue-specific histone code associated with obesity?

Epigenetic analysis (‘epigenomics’) refers to the study of DNA methylation and histone modifications that result in
altered gene expression. Overall, it is likely that epigenetic modifications, together with the genetic background of an individual, dictate the expression level of most genes and thereby the risk for disease. Recent studies have shown that inflammation can induce epigenetic alterations in tissues that prepare the ground for disease manifestation. Histones play a key role in the epigenetic control of gene transcription, and modification of histones either by acetylation or methylation can affect gene expression; histone acetylation, driven by enzymes termed histone acetyltransferases (HATs), is usually associated with gene activation, whereas histone methylation, driven by HDACs, results in different outcomes depending on the modified residue [55–57]. HAT action weakens the interaction between histones and DNA. By contrast, HDAC action stabilizes chromatin structure, consistent with the fact that HDACs are core enzymatic subunits of many corepressor complexes.

An emerging theme from several studies investigating the SMRT/NCOR/HDAC3 corepressor complex is that histone deacetylation represses inflammatory gene expression in both macrophages and adipocytes [58,59]. Of interest but currently poorly understood is the notion that the existence of promoter- and cell type-specific HDAC3 subcomplexes with NCOR and SMRT permit specific and sometimes opposing functions. In adipocytes, NCOR seems to be mainly involved in the repression of PPARγ pathways whereas SMRT, together with GPR2, appears to repress inflammatory gene transcription [34,48,50]. Notably, recent studies have shown that HDAC3 is involved in the regulation of macrophage polarization, suggesting that HDAC3 might act as an ‘epigenomic brake’ in macrophage activation [60]. Specifically, HDAC3-deficient macrophages are unable to activate inflammatory gene expression upon stimulation with cytokines. Intriguingly, HDAC3 also plays crucial role in the regulation of NF-κB pathways by directly deacetylating RelA (a non-histone target) and promoting its interaction with IkB, thus leading to its nuclear export and termination of NF-κB signaling.

Genome-wide maps of histone modifications coupled with transcriptional profiling have revealed which histone modifications are linked with either active or inactive transcription programs. Methylation of lysine 4 (H3K4) or lysine 36 (H3K36) on histone H3 is associated with transcribed chromatin, whereas methylation of lysine 27 (H3K27) and/or lysine 9 (H3K9) generally correlates with repression [61]. Although progress has been made in monitoring the state of histone modifications during adipogenesis in vitro [62], studies that clearly link such alterations to obesity in vivo are lacking. For example, loss of the enzyme Jhdm2a (also known as Kdm3a), a H3K9-specific demethylase, promotes adiposity and obesity without any nutritional challenge; demethylation of K9 by Jhdm2a facilitates the recruitment of receptors, such as PPARγ, and their coactivators to promoter sites of gene that drive the adipogenic program. Thus, H3K9-specific demethylation initiates a cascade of transcriptional changes that promote an increase in adipogenesis and repress adipose tissue inflammation [63].

CpG methylation (methylation at a cytosine preceding a guanine) is generally linked to transcriptional silencing via functional cooperation with repressive chromatin modifiers (e.g., HDACs, methylases). Although a direct association between alterations in DNA methylation and adipose tissue inflammation has never been clearly demonstrated, emerging data suggest that this might be a possibility. Notably, Bouchard et al. [64] have provided the first evidence that DNA methylation in adipose tissue differs between people who respond well and those who respond poorly to caloric restriction upon weight loss. Most recently, Ronn et al. [65] have shown that exercise influences DNA methylation not only in muscle but also in human adipose tissue, which interestingly affects the expression of SMRT. This suggests that exercise-mediated alterations of the DNA methylome have the potential to influence adipose tissue inflammation in humans.

To understand better the causal relationship between epigenomic alterations and obesity-associated chronic inflammation we will need to establish whether and which of the epigenomic changes precede the development of obesity or vice versa. Perhaps some alterations may not be causal at all, and are instead consequences of confounding factors such as nutrition, physical activity, gut flora diversity, and smoking.

**Epigenomic regulation via non-coding RNA: new players in adipose tissue inflammation**

Small non-coding RNAs termed microRNAs (miRNAs) are key post-transcriptional regulators of gene expression. They represent another important class of epigenomic regulators that functionally intersect with the genomic and epigenomic mechanisms of inflammatory processes described above [66]. Support for an integral role of miRNAs in adipose tissue development and function came from studies demonstrating that inhibition of miRNA actions in adipocyte progenitor cells represses the adipogenic process [67–69]. Following these pioneering studies, several reports revealed a crucial role for miRNAs in obesity, via their regulation of pathways involved in lipid and glucose homeostasis, and more recently inflammation [70]. Notably, many miRNAs appear to be differentially expressed in the adipose tissue of lean and obese subjects [71,72]. In addition, some miRNAs seem to be regulated by the inflammatory environment such as elevated levels of TNFα. Arner et al. recently reported that a subset of miRNAs were involved in the regulation of inflammatory pathways controlling the expression and secretion of chemokine (C-C motif) ligand 2 (CCL2) in human adipocytes and macrophages [73]. All these studies emphasize the importance of further exploring the role of miRNAs in the regulation of inflammatory processes in adipose tissue. In addition, the discovery that miRNAs circulate in the blood highlights their potential to be used as endocrine signaling molecules and disease biomarkers for obesity complications (diabetes and/or non-alcoholic steatohepatitis, NASH) and adipose tissue perturbations [72].

Another class of non-coding RNAs named enhancer-associated RNAs (eRNAs) has recently been discovered and linked to inflammatory gene expression. Two pioneering studies, employing mouse primary neurons and
macrophages as models, indicate that, upon activation, thousands of enhancer regions distant from the transcription start-sites recruit RNA polymerase II, thus allowing local transcription and synthesis of eRNAs [74,75]. In macrophages, eRNAs appears to influence the transcription of the chemokine CCL5, which may also occur in adipose tissue where CCL5 is known for its involvement in inflammatory cascades [76]. Most interestingly, Glass and coworkers demonstrated that eRNA transcription can be repressed by the nuclear orphan receptor Rev-ErbA, resulting in the repression of inflammatory genes such as Mmp9 and Cxc3cr1 in macrophages. This new regulatory cascade has not yet been investigated in adipose tissue but could present an alternative pathway to control obesity-associated inflammation.

Of men, not mice

As highlighted in this review, tissue-specific knockout mouse models have provided and will continue to provide powerful tools to dissect complex pathways. However, there is growing awareness of the limitations of using mouse models to decipher inflammatory pathways and identify drug targets related to obesity, as initially pointed out by Arner et al. [77]. More recently, a study entitled ‘Genomic responses in mouse models poorly mimic human inflammatory diseases’ [78], provoked the current debate on this issue. Differences between rodents and humans have been observed regarding the action of major cytokines that are implicated in adipocyte inflammation. TNFα is massively produced by adipose tissue of obese mice and released into the circulation to promote insulin resistance [79]. However, in humans, TNFα is not released into the circulation but has a local effect on adipocyte lipolysis [80]. Another example is that adipose tissue contributes to an increase in circulating IL-6 in humans, and elevated levels of IL-6 are strongly correlated with insulin resistance [81]. By contrast, IL-6 knockout mice develop insulin resistance and impaired glucose metabolism [82]. Collectively, these findings highlight the need to assess critically the relevance of findings from rodents to human physiology, and thus observations in rodent with regards to adipose tissue inflammation need to be taken into careful consideration. However, for the purposes of this review we have specifically highlighted genomic and epigenomic pathways that were characterized in human adipose tissue, and so far there is no evidence that these pathways are substantially different in mice.

Concluding remarks and future perspectives

The concept of metaflammation generally describes the interconnection between metabolic and inflammatory processes, and is particularly useful in characterizing the unique features of metabolically driven low-grade chronic inflammation in the context of obesity. Appreciating this connection leads to many exciting ideas and unanswered questions that need to be addressed in the future. For example, weight loss induced by gastric bypass surgery or caloric restriction is known to improve insulin resistance and type 2 diabetes [83,84]. This improvement is associated with a reduction of low-grade inflammation at the systemic and tissue levels, with a switch towards macrophage M2 phenotypes (anti-inflammatory) [23], and with restored expression of anti-inflammatory transcription factors (PPARγ, TWIST1, KLF4) [37,85] and corepressors (GPS2, SMRT) [34]. However, is reduction of inflammation the consequence of the metabolic improvements, or is the opposite causality more likely? Such questions are fundamental because answering them will provide insights into mechanisms that promote and, upon intervention, reverse or even prevent adipose tissue inflammation in obesity. Clearly, more detailed insights into the series of transcriptional events underlying the inflammatory switch following weight loss are required.

As another example, it was recently reported that a subgroup of diabetic subjects treated with the PPARγ agonist pioglitazone did not improve their inflammatory status of adipose tissue whereas their glycemic status was ameliorated [34]. Would the study of these subjects reveal some of the missing molecular links between metabolic and inflammatory regulation in adipose tissue? Would it perhaps reveal specific transcriptomic and epigenomic signatures that can be further exploited to predict clinical responses to TZDs and other types of anti-inflammatory drugs?

Thus far, therapeutic strategies that rely on targeting single cytokines or receptors (e.g., TNFα and IL-1) have met with limited success in humans [86,87], suggesting that targeting downstream signaling and transcriptional components rather than circulating cytokines could provide a more effective therapeutic approach. However, a general concern with broad anti-inflammatory therapies has been that they could adversely compromise immune system responses. To overcome this problem, inhibition of JNK, IKK, or TBK1 activation under conditions of chronic inflammation emerges as a promising strategy [14,88].

Alternative strategies may selectively target transcriptional components, thus affecting the herein-discussed genomic and epigenomic components of inflammation control. Nuclear receptors including GR, PPARs, and LXRs are powerful transcriptional integrators of inflammation and metabolism, and are well-established targets for anti-inflammatory drugs [54]. The challenging task will be to develop improved drugs that do not interfere with the beneficial metabolic function, thus performing in a highly pathway- and cell type (adipocytes, macrophages, and liver)-specific manner.
In addition, epigenetic drugs such as inhibitors of HDACs or demethylases emerge as players not only in cancer but also in the management of inflammation. In particular, the anti-inflammatory action of NCOR/SMRT/GPS2/HDAC3 subcomplexes in adipose tissue (i.e., in adipocytes and macrophages) could represent a novel target to limit chronic inflammation, alone or in combination with anti-inflammatory nuclear receptor ligands. Notably, recent synthetic compounds have been reported to modulate specifically the function of HDAC subcomplexes [89]. Provided that these and other epigenomic regulators are likely considerable players in adipose tissue, future efforts will need to scrutinize their therapeutic potential in the context of obesity-associated inflammation.

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References

14 Han, M.S. et al. (2013) JNK expression by macrophages promotes obesity-induced insulin resistance and inflammation. Science 339, 218–222
15 Han, N. et al. (2011) Deficiency in interferon-gamma results in reduced body weight and better glucose tolerance in mice. Endocrinology 152, 3690–3699
18 Wang, X.A. et al. (2013) Interferon regulatory factor 9 protects against hepatic insulin resistance and steatosis in male mice. Hepatology 58, 603–616
27 Cipolletta, D. et al. (2012) PPAR-gamma is a major driver of the accumulation and phenotype of adipose tissue Treg cells. Nature 486, 549–553

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56 Talas, H. et al. (2005) Histone H4 lysine 20 monomethylation is increased in promoter and coding regions of active genes and correlates with hyperacetylation. J. Biol. Chem. 280, 38814–38822


58 Li, J. et al. (2000) Both corepressor proteins SMRT and N-CoR exist in large protein complexes containing HDAC3. EMBO J. 19, 4342–4350


60 Mulligan, S.E. et al. (2011) Histone deacyetylase 3 is an epigenomic brake in macrophage alternative activation. Genes Dev. 25, 2480–2488


67 Bengestrade, L. et al. (2011) Genome-wide profiling of microRNAs in adipose mesenchymal stem cell differentiation and mouse models of obesity. PLoS ONE 6, e21206


76 Wang, D. et al. (2011) Reprogramming transcription by distinct classes of enhancers functionally defined by eRNA. Nature 474, 390–394

77 Arner, P. (2005) Resistent: yet another adipokine tells us that men are not mice. Diabetologia 48, 2203–2205


82 Wallenius, V. et al. (2002) Interleukin-6-deficient mice develop mature-onset obesity. Nat. Med. 8, 75–79


88 Calay, E.S. et al. (2013) Turning off the inflammatory, but not the metabolic, flames. Nat. Med. 19, 265–267


94 Deng, T. et al. (2013) Class II major histocompatibility complex plays an essential role in obesity-induced adipose inflammation. Cell Metab. 17, 411–422
