Seminars in Immunopathology (2019) 41:515–529
https://doi.org/10.1007/s00281-019-00748-1

REVIEW

Transcriptional control of macrophage polarisation in type 2 diabetes

Karima Drareni[1] · Jean-François Gautier[1,2] · Nicolas Venteclef[1] · Fawaz Alzaid[1]

Received: 18 March 2019 / Accepted: 18 April 2019 / Published online: 2 May 2019

Abstract

Type-2 diabetes (T2D) is considered today as an inflammatory disease. Inflammatory processes in T2D are orchestrated by macrophage activation in different organs. Macrophages undergo classical M1 pro-inflammatory or alternative M2 anti-inflammatory activation in response to tissue microenvironmental signals. These subsets of macrophages are characterised by their expression of cell surface markers, secreted cytokines and chemokines. Transcriptional regulation is central to the polarisation of macrophages, and several major pathways have been described as essential to promote the expression of specific genes, which dictate the functional polarisation of macrophages. In this review, we summarise the current knowledge of transcriptional control of macrophage polarisation and the role this plays in development of insulin resistance.

Keywords Inflammation · Diabetes · Macrophage · And transcription

Introduction

The innate immune system permeates every tissue of the human body, representing the body's first line of defence [1]. Component cells of innate immunity elicit rapid and non-specific responses to danger signals and presenting antigens to cells of the adaptive immune system. Under physiological circumstances, macrophages form the majority of tissue immune cells, carrying out homeostatic roles such as clearing dead cells and signalling tissue damage [2]. Dysregulated over-exuberant responses, often in the form of sterile inflammation, arise from macrophages and form part of virtually every human disease, including T2D [1]. During the development of T2D extensive studies have shown that adipose tissue macrophages are central to the onset of insulin resistance and diabetic pathogenesis [3]. Similarly, an increasing number of studies show that macrophages in other tissues also undergo inflammatory polarisation and are key mediators of diabetic complications and comorbidities [4] (see review in this issue). Macrophages were classically considered to exist in three polarisation states, M0 (quiescent), M1 (pro-inflammatory) and M2 (anti-inflammatory). However, these states are no longer considered discrete, rather M0, M1 and M2 states exist on a graduated scale that better represents the plasticity and dynamic nature of macrophage responses [5]. Nonetheless, it is well established that in T2D the inflammatory hit, key to pathogenesis, is mediated by M1 polarised macrophages. Furthermore, tissue-dependent contexts either result in an increasingly pro-inflammatory milieu (e.g. adipose tissue, pancreas) or pathologic M2 polarisation (e.g. liver, large vessel walls). The maladapted M2 polarisation is pathologic because an M2 polarisation not only denotes resolving inflammation, but also an exuberant scarring response and the laying down of fibrous matrix that may affect organ function (major component of liver fibrosis and atherosclerotic plaques) [6]. Given the divergent macrophage phenotypes that did not neatly represent behaviour of the effector cells observed in metabolic inflammation, the M1/M2 paradigm had been further readdressed, leading to discovery of a functionally and phenotypically distinct subset of metabolically activated macrophages (MMe) [7]. The MMe was classified in 2014 by Kratz et al., notably, MMes respond to metabolic stimuli (palmitate, free fatty acids) and express specific cell surface proteins (ABCA1, CD36 and PLIN2). These membrane proteins not only allow MMes to be phenotypically characterised but also

This article is a contribution to the special issue on Inflammation and Type 2 Diabetes - Guest Editor: Marc Y. Donath

✉ Nicolas Venteclef
nicolas.venteclef@inserm.fr

✉ Fawaz Alzaid
fawaz.alzaid@inserm.fr

[1] Cordeliers Research Centre, INSERM, Immunity and Metabolism in Diabetes Laboratory, Sorbonne Université, USPC, Université Paris Descartes, Université Paris Diderot, F-75006 Paris, France

[2] Lariboisière Hospital, AP-HP, Diabetology Department, University of Paris Diderot, Paris, France

allows MMes to carry out functions associated with handling metabolic stressors [7, 8]. In this light, divergent roles have been reported for MMes, including the upregulation of inflammatory signalling leading to tissue damage and systemic inflammation, as well as the clearance of senescent adipocytes to prevent ectopic fat storage. In the case of MMes the balance between inflammatory signalling, lysosomal exocytosis (typically M2 associated response) and the expression of their functional and phenotypic receptors is transcriptionally controlled [8]. This transcriptional control overlaps to a certain degree with the canonical pathways described in M1 and M2 macrophages, notably in the activation of nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB) protein and subsequent inflammatory signalling. Conversely, MMes are also capable of intrinsically repressing NF-κB signalling through p62 and peroxisome proliferator-activated receptor-γ (PPAR-γ) dependent mechanisms. The phenotypic transitions of macrophages, M1 to M2 and MMe, are all dependent on transcriptional reprogramming. Such events are dependent on signalling cascades downstream of cell surface receptors (namely pattern recognition receptors, or PRRs). PRR stimulation leads to intracellular events that differentially activate nuclear receptors and transcription factors [9, 10]. Once polarisation is engaged, negative and positive feedback loops are responsible for phenotypic shifts resolving or sustaining inflammation. Interestingly, even maintenance of an unpolarised state is transcriptionally mediated, largely through post-translational mechanisms and chromatin features that silence transcriptional programmes associated with macrophage polarisation [11]. This review discusses the mechanisms through which macrophage polarisation is regulated, from cell surface receptors to epigenetic mechanisms, in the context of metabolic inflammation. Notably, we review the most pertinent mechanisms that contribute to inflammatory pathogenesis of T2D and the progression of diabetic complications. The macrophage subsets discussed in this review are those infiltrating in adipose tissue, the liver and vasculature. Recent research has significantly widened the knowledgebase with regards transcriptional mechanisms of activation of these tissue macrophages. Other tissues important in diabetic pathogenesis, such as the pancreas, are not discussed in this review due to the scarcity of recent research in the transcriptional control of pancreatic macrophage activation.

TLR-dependent pathways in T2D

Toll-like receptors are members of the pattern recognition receptor superfamily of proteins. They are an ancient class of transmembrane non-catalytic receptors expressed on and in sentinel cells (innate immune cells such as macrophages as well as non-immune cells to signal danger). Their high conservation is due to selective evolutionary pressure to recognise and defend of against structurally conserved molecules from pathogens [12]. Despite the canonical role of TLRs in host defence against pathogens, several TLRs (and their downstream signalling cascades) have been implicated in metabolic inflammation, insulin resistance and T2D [13, 14]. This means that TLRs do not only recognise infectious pathogens, but also metabolic stressors or damage signals associated with the sterile inflammation. To date, two TLRs that have been repeatedly linked to T2D pathogenesis: TLR2 (including its heterodimerisation to TLRs 1 and 6) and TLR4. These TLRs both give rise to chronic inflammation and decrease insulin sensitivity through interfering with components of the insulin-signalling pathway. Downstream signalling from TLR2 and TLR4 associated with T2D share common pathways that elicit inflammatory polarisation, or a type-1 immune response, in macrophages. These downstream signalling events include a number of signal transducers, kinases and activators of transcription setting in motion the transcriptional programmes under control of nuclear factor κB, activator protein-1 and IFN regulatory factors. TLR2 and TLR4 share a universal adaptor protein, the myeloid differentiation primary response 88 (MyD88) protein. MyD88 is an adaptor protein to all TLRs (except TLR3), Mal/TIRAP is necessary for MyD88 recruitment to TLRs 2 and 4, and further signal transduction occurs through IRAK [1, 14, 15]. The co-ordinated action of these TLRs and MyD88 results in activation of two principle transcription factors, AP1 and NFkB.

Signal transducers and activators of transcription

Signal transducers and activators of transcription (STATs) are a family of 7 transcription factors that form part of the interferon system. They have well-established roles in the development and function of the immune system, notably regulating apoptosis, proliferation and differentiation and maintaining immune tolerance. STAT activity is regulated by cytokines and growth factors, which once signalled to membranes initiate Janus kinase (JAK)-mediated phosphorylation of STATs allowing their dimerization and nuclear translocation. This cascade is referred to as the JAK-STAT pathway. STAT1 and STAT5 are known to induce M1 polarisation of macrophages whereas STAT3 and STAT6 are known to induce M2 macrophage polarisation; interestingly, the MMe phenotype polarises independently of STAT1 signalling [8]. Whilst STAT1 indeed has not been reported to play a role in macrophages in obesity and insulin resistance, in vitro and ex vivo studies have demonstrated that STAT1 is activated in response to high glucose where a large epigenetic component has been attributed to its function [16, 17]. Similarly, no conclusive studies

have linked STAT5 to T2D pathogenesis to our knowledge. By contrast, the M2 polarising STATs have been more closely associated to T2D and its complications. STAT3 is a downstream target of metformin. Metformin inhibits differentiation of monocytes to macrophages through AMPK-mediated inhibition of STAT3; this also resulted in decreased monocyte infiltration into atherosclerotic plaques and an ameliorated outcome in mice [18]. Similarly, anti-inflammatory polarisation ABCA1/APOA-I activity was found to be STAT3-dependent [19]. With regard to M2 polarising STATs, in a model of myeloid-specific deficiency of JAK2, reduced phosphorylation of STAT3 led to a less inflammatory and healthier visceral adipose tissue phenotype upon diet-induced obesity and insulin resistance [20]. Similarly, the M1 polarisation that VASP (vasodilator-stimulated phosphoprotein)-deficient macrophages undergo is dependent upon STAT6 signalling, this pro-inflammatory VASP-STAT axis induces hepatic inflammation and insulin resistance [21]. Mice deficient for STAT6 are more prone to diet-induced obesity and increase in oxidative stress and inflammation in adipose tissue, increasing susceptibility to insulin resistance and T2D [22]. Of the STATs involved in macrophage polarisation, STAT3 and STAT6 have been implicated in buffering pro-inflammatory polarisation throughout diabetogenesis; with no M1 polarising STAT being shown as a major contributor to metabolic inflammation.

Pro-inflammatory transcriptional machinery: NF-κB and AP-1

Two main transcription factor complexes orchestrate macrophage inflammatory polarisation in contribution to T2D pathogenesis. Activator protein 1 (AP-1) and nuclear factor κB (NF-κB). Both complexes are known to promote an M1 phenotype in macrophages [23, 24]. *AP-1* is a heterodimer composed of a number of proteins, notably the proto-oncogenes c-Jun, c-Fos that are essential for DNA binding [25]. AP-1 regulates cell growth, differentiation, apoptosis as well as other cellular processes, in response to physiological stress [26]. AP-1's activity is regulated by post-translational modifications, composition of its DNA binding dimer and through interactions with various binding partners [27]. The c-Jun subunit is phosphorylated by the c-Jun N-terminal kinases (JNKs) that belong to the mitogen-activated protein kinase family (MAPK). Cell extrinsic stimuli that regulate AP-1 activity include cytokines and growth factors (as well as typical PRR ligands such as bacterial and viral stimuli). In the context of T2D and its vascular complications, palmitate, as a source of long-chain saturated fatty acids (SFAs), has been shown to activate AP-1 in macrophages as well as the downstream release of pro-inflammatory cytokines [15]. Interestingly, only a limited subset of these cytokines was mediated through MyD88-dependent mechanisms described above [15]. Moreover, leptin has been reported to increase binding to the AP-1 consensus sequence of lipoprotein lipase gene in macrophages, a gene known to promote foam cell formation and the development of aortic lesions [28]. JNK has been extensively investigated in obesity and insulin resistance. Mice deficient for JNK1 and/or JNK2 are protected from diet-induced obesity, inflammation, and insulin resistance (implicating JNK in metabolic inflammation as well as maintaining energy balance) [29, 30]. Targeting myeloid cells revealed that JNK deficiency results in non-inflammatory obesity as well as decreased serum free fatty acid levels, indicating a role for JNK in adipose tissue macrophage control over lipolysis [31]. *NF-κB* is similarly a ubiquitously expressed protein complex that controls transcription in response to a number of stress stimuli. NF-κB is well documented to initiate cytokine production and control cell survival under physiological stress (cytokines, free radicals, oxidised LDL, bacterial and viral stimuli) [32, 33]. Dysregulated NF-κB signalling has been reported in a number of inflammatory conditions, including T2D. In the context of T2D, NF-κB is highly expressed in adipose tissue macrophages upon their pro-inflammatory polarisation and during the development of insulin resistance. Moreover, cytokine secretion by these M1/MMe macrophages results in NF-κB activation in other leukocytes recruited to the site of inflammation, increasing magnitude of the inflammatory hit in T2D. Murine models deficient for inhibitor of nuclear factor kappa B kinase (IKK-β, NF-κB's canonical activator protein) in myeloid cells show a diminished inflammatory response upon high-fat feeding and retain global insulin sensitivity. Interestingly, the model with a hepatic deficiency of IKK-β only retains insulin sensitivity in the liver (not in muscle not in adipose tissue) [34]. This indicates that the NF-κB/IKK-β cascade in myeloid cells is major determinant of global-peripheral insulin resistance in T2D.

Interferon regulatory factors and the type-1 interferon response in T2D

Interferon regulatory factors (IRFs) are a family of transcription factors renowned for their control over the type-1 interferon response. Although initially discovered for their binding to virus-inducible enhancer elements on interferon coding genes, studies have revealed diverse roles of IRFs in T2D, in cells of the innate immune system as well as metabolic cells (e.g. adipocytes) [35, 36]. The 9 members of the IRF family (named simply IRF1 to IRF9) vary between 300 and 500 amino acids in length and share a conserved N-terminal DNA binding domain that allows binding to interferon consensus domains located upstream of interferon genes. The C-terminal region is variable and contains IRF-association domains that allow interactions between the different IRFs [37].

Six out of the 9 members are known to be involved in macrophage differentiation and polarisation (IRFs 1-5 and IRF9) [36]. Extensive studies in metabolic diseases have been carried out on IRF4 and IRF5 solidifying their roles in the pathogenesis of T2D [36]. Macrophage terminal differentiation to a pro-inflammatory state is dependent upon IRF5, whereas commitment to an anti-inflammatory state is controlled by IRF4 [38]. Accordingly, these polarisation states, and their transcriptional induction, have been found to be of profound importance in adipose tissue macrophages. IRF5 in particular has been found to be instrumental in mediating metabolic inflammation, leading to perturbed adipose tissue expansion and the development of insulin resistance [39]. Of note, IRF5 is the direct effector downstream of TLR4 in textbook immunology (i.e. viral or bacterial stimuli); however, the TLR4-IRF5 axis remains to be thoroughly investigated in metabolic hits and the pathogenesis of T2D. Phenotypically, the deficiencies of IRF5 or TLR4 are almost identical, mice gain weight upon high-fat feeding yet adipocytes remain small and insulin sensitive, leading to a non-inflammatory obesity and conserved peripheral sensitivity to insulin [40]. This phenomenon, in the case of IRF5 deficiency is mediated by alternatively activated macrophages that restrict adipocyte growth and promote a hyperplasic and metabolically protective response upon diet-induced obesity. Of equal importance, IRF5 has also been found to play important role in the development of the hepatic comorbidities of diabetes, namely NASH [41]. IRF5 is required for pro-apoptotic signalling associated with hepatotoxicity or hepatocyte lipotoxicity. Of note, the metabolic phenotype in IRF4 deficiency is in opposition to IRF5 deficiency, as expected from the negative regulatory of inflammation in macrophages [42]. IRF4 deficiency in myeloid cells, results in mice with exuberant adipose tissue inflammation and decreased insulin sensitivity when compared to IRF4-competent mice upon diet-induced obesity despite no differences in weight gain [42]. IRF5 is required for optimal expression of IL-12 and other pro-inflammatory cytokines. These findings, initially in mice, have been reproduced in human macrophages primed with granulocyte–macrophage colony-stimulating factor (GM-CSF) [43, 44]. IRF5 is directly recruited to gene promoters associated with the M1 phenotype (including IL-12b and Tnf), but it also plays a repressive role, targeting type-2 effector molecules (IL-10, TGF-β) [39, 41, 45]. A similar approach confirmed and extended this mechanism in human adipose tissue macrophages, indicating that the protective phenotype observed in IRF5 deficient mice is largely due to the derepression of these anti-inflammatory and metabolically protective genes [39, 41]. An interesting aspect of these studies is the dual function of IRF5 in activating M1 genes whilst repressing M2 genes by binding to similar *cis*-acting elements as IRF4 in the gene promoters. This indicates that there might be different collaborating TFs and/or coregulators for IRF5 at M1 versus M2 gene promoters, and that these factors might direct distinct functional outcomes. A pioneering study demonstrated that NF-κB subunit, RelA (p65), assists IRF5 in binding to DNA, and the two TFs set up a unique "inflammatory" IRF5:RelA cistrome [44]. This mechanism is key in the regulation of M1 polarisation genes. Regarding the repressive action, which is more clinically relevant, important work is needed to identify partners of IRF5 in specific pathologic contexts which will lead to defining novel therapeutic targets. The interactome of IRF5 is rapidly expanding and it is possible that other yet to be identified TFs or coregulators may participate in recruitment of IRF5 to specific gene promoters. In addition, it is of clinical relevance that human genome-wide association studies identified a number of IRF5 risk variants to be associated with autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease [46–48].

Nuclear receptors in the regulation of macrophage polarisation in T2D

Macrophages are known to express a wide range of nuclear receptors (NRs) such as peroxisome proliferator-activated receptors (PPARs), liver X receptor (LXR) and glucocorticoid (GC) receptors. Different studies have shown the important roles for NRs in controlling programmes of macrophage gene expression and polarisation in a tissue specific manner. In macrophages, NRs (such as GR, PPARs and LXRs) regulate inflammatory pathways controlled mainly by AP-1 and NF-κB.

Peroxisome proliferator-activated receptors

PPARs are ligand-activated transcription factors. In mammals, there are three PPAR subtypes (PPARα, γ and δ/β). PPARs are expressed in a variety of metabolic tissues and cell types, including immune cells. The PPARs are implicated in various cell functions such as metabolic processes and cell differentiation. In the last few years, PPARs have also emerged as key regulators of inflammatory and immune responses.

PPAR-α In classically activated M1 macrophages, PPAR-α activation inhibits the production of pro-inflammatory molecules such as MMP-9 by negatively regulating the AP-1 and NF-κB signalling pathways. Effects of PPAR-α on MMP-9 may account for the beneficial effect its agonists have shown in diabetic atherosclerosis [49]. Furthermore, in patients with T2D, PPAR-α has been shown to reduce the expression of osteopontin (OPN) in macrophages. OPN is a pro-inflammatory cytokine implicated in the chemoattraction of monocytes and the development of atherosclerosis [50]. Similarly, treatment of T2D patients with PPAR-α agonists has shown successful reduction of plasma OPN. PPAR-α in

the macrophages seems to inhibited OPN expression by inhibiting c-Fos and phospho-c-Jun (and thus AP-1) binding to the OPN promoter [50]. Another study has shown that PPAR-α agonists attenuate oleate-induced total FFA and TG accumulation in the macrophages, which represses pro-inflammatory pathways. The activation of PPAR-α suppresses FATP1 (fatty acid transporter) expression in macrophages. Thus, activating PPAR signalling, and repressing FFA import and triglyceride synthesis, is a promising approach to reduce the risk of obesity, T2D and more importantly atherosclerosis as a complication of T2D [51]. The anti-inflammatory actions of PPAR-α have been characterised in both in human and murine macrophages; however, a number of target genes are differentially regulated between species.

PPAR-β/δ PPAR-β/δ has also been reported to be involved in the regulation of macrophage lipids efflux by controlling beta-oxidation, energy dissipation, FFA catabolism and the homeostasis of VLDL-derived fatty acids, playing a key role in lipid-related disorders, including dyslipidaemia and diabetes [52]. In addition, in the context of obesity and T2D, PPAR-β/δ has been reported to play a major role in macrophage infiltration and polarisation in adipose tissue and liver. The signalling of Th2 cytokines released by adipocytes induces PPAR-β/δ through signal transducer and activator of transcription 6 (STAT6) binding on its promoter leading to alternative activation of macrophages. The switch to the M2 phenotype prevents the inflammation caused by inflammatory factors, such as FFA, in adipose tissue and liver. In agreement with this model, myeloid-specific PPAR-$\beta/\delta^{-/-}$ mice develop insulin resistance and show increased adipocyte lipolysis and severe hepatic steatosis [53].

PPAR-γ All the studies that have investigated the role of PPAR-γ in the macrophages have come to the conclusion that PPAR-γ activation leads to the inhibition of macrophage polarisation and thus to anti-inflammatory properties in both human and murine monocytes/macrophages. In human activated macrophages, PPAR-γ reduces MMP-9 activity and inhibits IL-1β, IL-6 and TNF-α expression [49, 54, 55]. In murine macrophages, PPAR-γ activation represses the induction of several inflammatory response genes (induced by LPS and IFNγ), including iNOS, COX-2, and IL-12 [56–58]. Different mechanisms may be involved in the repression of inflammatory genes by PPAR-γ. One of the best-characterised mechanisms is the transrepression by which NRs bind directly to transcription factors (NF-κB, AP-1 …) and modulate their transcriptional activity. PPAR-γ can inhibit inflammatory responses by blocking the signal-dependent clearance of the nuclear receptor corepressor (NCoR) complexes [59]. This mechanism involves SUMOylation of PPAR-γ, thus facilitating interactions with the NCoR complex [60]. PPAR-γ has also been shown to enhance the differentiation of monocytes into alternatively M2 activated macrophages, induced by Th2 cytokines, such as IL-4 and IL-13 [61, 62]. Consequently, inhibition of PPAR-γ specifically in macrophages in mice leads to the impairment in the maturation M2 macrophages and exacerbation of diet-induced obesity, insulin resistance, glucose intolerance, and expression of inflammatory genes [62, 63]. Consistent with this idea, administration of PPAR-activating TZD (Thiazolidinedione) reduces inflammation in murine models of obesity and T2D [64].

Liver X receptors

LXRs are lipid-activated transcription factors expressed in numerous cell type including macrophages. There are 2 isoforms of LXR (LXR-α and LXR-β). Both LXR isoforms regulate macrophage inflammatory responses. LXRs modulate gene transcription by heterodimerising with the retinoid X receptor (RXR) and binding to the LXR response elements (LXREs) in the transcriptional regulatory regions of their target genes [65]. Activation of LXR by certain oxysterols and synthetic compounds leads to cholesterol efflux from macrophages through the transcriptional upregulation of ATP-binding cassette (ABC) transporters, such as ABCA1 and ABCG1 [66]. Different studies have identified LXRs as regulators of inflammatory response both in human and murine macrophages. Indeed, LXRs have been shown to inhibit the transcription of pro-inflammatory genes such as IL6, IL1-β, MCP1, iNOS and others after pro-inflammatory stimuli [67]. Moreover, a recent study has shown that LXRs can also induce the expression of arginase-2, an anti-inflammatory enzyme that uses the same substrate as iNOS [68]. The mechanism involved in the repression of inflammatory genes by LXRs are believed to be the same ones induced by the PPARs; the transrepression of pro-inflammatory transcription factors NF-κB or AP-1 without directly binding to DNA. In a recent study aiming to understand transrepression of the iNOS and IL-1β promoters by LXRs, SUMOylation of LXRs was identified as a possible mechanism involved in this process. Sumoylated LXR was suggested to prevent LPS-dependent exchange of corepressors for coactivators, thus maintaining the iNOS promoter in a repressed state [69]. The ability of LXR to control macrophage-mediated inflammation by these mechanisms appears to have an important impact on the control of insulin resistance since the beneficial effects of weight loss on obesity-related insulin resistance are associated with an improved inflammatory profile.

Glucocorticoids receptors

Glucocorticoids (GCs) are steroid hormones that are involved in different physiological process by regulating gene transcription and are essential for maintenance of homeostatic

functions. The GCs are secreted from the adrenal gland in response to different stressors. Their effects are mediated by the glucocorticoid receptor (GR), a member of the nuclear receptor superfamily. The activation of the GR by its GC ligands leads to the nuclear translocation of the ligand-receptor complex, promoting or repressing the transcription of target genes by direct binding to DNA response elements and/or by interacting with other TFs such as NF-κB or AP-1 and repressing their action [70]. The action of GCs has been widely recognised as anti-inflammatory and immunosuppressive. Microarray analysis of human macrophages treated with GCs demonstrated significant upregulation of anti-inflammatory genes (IL-4, IL-10) and down-regulation of pro-inflammatory genes (IL-1, IL-6, and TNF-α) [71]. Moreover, GCs have been shown to promote an M2 phenotype by inducing a subpopulation of M2 macrophages (M2c macrophages). The M2c cells are involved in different processes that are essential for wound healing and resolution of inflammation. However, this effect seems to be dependent on the type of Th cytokine environment and on the stage of monocyte-to-macrophage differentiation. Indeed, exposure of human monocytes/macrophages to GR, can either lead to apoptosis or differentiation into regulatory M2c macrophages. The presence of IFN-γ or the prolonged exposure to IL-4 promotes apoptosis of monocytes/macrophages, provoking impaired clearance of apoptotic neutrophils, uncontrolled accumulation of apoptotic cells, and persistent inflammation. In contrast, the presence of IL-17 prevents monocyte/macrophage apoptosis and induces M2c differentiation, leading to the restoration of anti-inflammatory conditions [72]. GC activation of nuclear receptors alters the interaction of AP-1 and NF-κB proteins with coactivator complexes required for initiating transcription. In the case of NF-κB, activated GR binds its p65 subunit impairing formation of the NF-κB-IRF complex [73]. GR can also regulate the inflammatory response by inducing the expression of proteins that block pro-inflammatory pathways. GCs have inhibitory effects on the MAPK signalling pathways through MAPK phosphatase-1, which inhibits p38 MAPK, preventing the induction of multiple inflammatory genes [74]. Even though the impact of GR on the adipocytes, adiposity and insulin resistance has been more or less well characterised and also seems to be context dependent [75], their impact on macrophages in the obesity and insulin resistance is relatively poorly understood.

Hypoxia-inducible factor 1

Hypoxia-inducible factor 1 (HIF1) is a transcription factor composed of α and β subunits. HIF1-β is constitutively expressed and stabilised in cells independently of O_2 levels. HIF1-α protein is only stabilised and increases in response to hypoxia (low O_2 levels) [76]. HIF1-α is then translocated to the nucleus where it heterodimerizes with HIF1-β and activates its target genes. HIF1 has displayed a significant role in regulating cellular metabolism, in particular glucose metabolism [77]. As glucose metabolism determines polarisation of macrophages, it has been reported that HIF1 plays a key role in the regulation of macrophage polarisation [78]. In addition, hypoxia has been shown to induce a profound change in gene expression profiling of macrophages and monocytes [79]. Recently, a study has shown that murine myeloid-specific HIF1-α overexpression leads to a hyper-inflammatory state characterised by the upregulation of M1 markers and polarisation. It seems that this phenotype was the result of upregulation of the expression of glycolysis genes in macrophages by HIF1, in accordance with these results; the deletion of HIF1-α in myeloid cells also revealed that HIF1-α is essential in regulating myeloid cell glycolytic capacity and therefore function in an inflammatory microenvironment. HIF1-α is also known to be decreased in adipose tissue by obesity leading to an aggravation of the pro-inflammatory profile. It has been reported that adipose tissue hypoxia induces inflammatory M1 polarity of macrophages in a HIF1-α dependent and HIF1-α independent manner in obese mice. Hypoxia upregulates the transcription of inflammatory cytokines, such as TNF-α, IL-6 and IL-1β in vitro and in vivo. This effect could be reversed by deletion of HIF1-α. These results suggest that hypoxia induces the inflammatory phenotypes of macrophages, at least in part via HIF1-α-dependent mechanisms [80]. Another recent study has shown that myeloid cell-specific HIF1-α gene deletion protected against HFD-induced inflammation, crown-like structure (macrophages that surround senescent adipocytes in visceral adipose tissue) formation and systemic insulin resistance. In addition, it has been reported that HIF1-α induces the expression of various genes related to angiogenesis and fibrosis such as VEGF and MMPs that amplify the phenomenon of macrophage infiltration (diapedesis) into hypoxic regions in metabolic diseases like obesity, diabetes and atherosclerosis [81].

Transcriptional corepressor complexes: pro- versus anti-inflammatory actions

It is nowadays well known that the transcriptional coregulators play a key role in macrophage function and polarisation [82]. Under basal conditions the pro-inflammatory genes in the macrophages are maintained in an inactive transcriptional state by corepressor complexes residing at promoter or enhancer regions [83]. A pro-inflammatory hit such as LPS induces the clearance of such corepressor complexes leading to the activation of transcription of inflammatory genes and a subsequent inflammatory response. The major corepressors, NCOR and silencing mediator of retinoid and thyroid hormone receptors (SMRT), have been widely

involved in macrophage activation and polarisation [82]. As discussed above, anti-inflammatory signals, such as LXR and PPAR-γ, stabilise corepressor complexes to inhibit expression of inflammatory markers.

Inflammatory functions of NCOR and HDAC3 complex

Although NCOR is known to cause basal repression of inflammatory pathways [84], the specific deletion of NCoR in macrophages caused the de-repression of LXR, leading to the induction of lipogenic genes (i.e. *Elovl5*, *Fads2*, *Fasn*, *Scd1*, and *Scd2*). This in-turn causes increased biosynthesis of palmitoleic acid (POA) and ω3 fatty acids that, within macrophages, exert strong local anti-inflammatory effects by repressing NF-κB [85]. NCOR seems to exert pro-inflammatory actions in macrophages. Similarly to NCOR, it was surprising that macrophages from HDAC3 deficient phenotypes were anti-inflammatory in two independent studies [86, 87]. Whilst the possible involvement of the LXR/ω-3 fatty acid pathway along with high-fat diet treatment was not analysed in these studies, HDAC3 was shown to be required for the LPS/IFN-mediated induction of hundreds of pro-inflammatory genes. The requirement of HDAC3 for LPS/TLR4 responses, also observed in a number of earlier macrophage studies, seemed surprising given the assumed repressive role of HDAC3 as part of the complex. Indeed, in another study, HDAC3 and NCOR were shown to assemble a repressive complex via the NF-κB subunit p50, necessary for the TLR tolerance phenomena where sustained TLR4 activation represses inflammatory gene expression. Independently of the anti-inflammatory M1 phenotype, HDAC3-deficient macrophages showed an alternative M2-like phenotype in the absence of external stimuli. Thus, a likely role of HDAC3 is to repress M2 activation, perhaps by inhibiting STAT6/PPAR-γ activities. Overall, the involvement of HDAC3 in both M1 and M2 macrophage pathways raises the possibility of integrative crosstalk of the corepressor complex in mediating transcriptomic rewiring of macrophage fate.

Anti-inflammatory functions of GPS2 complex in human and mice

In contrast, the SMRT/GPS2 (G protein pathway suppressor-2) subunit/complex seems to have an anti-inflammatory function in the macrophages. In a recent study conducted by our team we have demonstrated that the specific knockout of the GPS2 subunit in macrophages induces an exacerbation of the pro-inflammatory profile leading to disturbed glucose homeostasis under metabolic stress [88]. The phenotype is consistent with the genomic features of the GPS2-containing repression pathway and involves direct repression of the c-Jun subunit of AP-1. During this study, we have shown that GPS2 was essential for the repression of the AP-1 complex and that GPS2 deficient macrophages exhibit an over-activation of the TLR4 pathway. Interestingly, earlier work had elucidated in detail the essential role of c-Jun in TLR4 signalling and regulating CCL2 expression and suggested direct interactions with HDAC3 and SMRT/NCOR. The proposal of two functional sub-complexes, that is, GPS2/SMRT (anti-inflammatory) versus NCOR/HDAC3 (pro-inflammatory), clarified the seemingly contradictory phenotypes of the corresponding KO models. The data put forward the concept that functional subcomplexes exist within what is commonly thought to function as "one corepressor complex". Subcomplex specificities would allow controlling transcription of distinct gene clusters in response to a variety of signals and likely result from differential interactions with TFs, coregulators, and chromatin components (e.g. histones).

Research into human disease mechanisms greatly benefits from clinical correlation data as they can provide the starting hypotheses that can subsequently be tested and validated in mice and cellular models. This is exemplified in our recent studies where we aimed at exploring which coregulators critically modulate metabolic inflammation in the context of obesity and T2D [88–90]. Gene expression analysis in macrophages isolated from adipose tissue of three different human populations revealed a significant decrease in GPS2, but not of any other corepressor complex subunit, in adipose tissue macrophages of diabetic subjects. Reduced GPS2 levels were correlated with an increase in markers of inflammation (notably CCL2, which subsequently was characterised as a major GPS2-regulated gene) and insulin resistance (HOMA-IR or HbA1c). These correlations are of importance because they point at the possibility that inappropriate GPS2 function could be linked to macrophage pathways that drive adipose tissue dysfunction and insulin resistance. Our study provides a unique example for how alterations of an epigenomic coregulator can influence the intensity of the inflammatory response toward T2D onset.

Repressive epigenetic marks and T2D: Example of the chromatin modifier JMJD3 (KDM6B) in macrophages

Aberrant epigenetic reprogramming occurs frequently in the development of diseases. Histone H3 lysine 27 trimethylation (H3K27me3) exerts a repressive epigenetic mark on a large number of genes. UTX and JMJD3 are the only histone demethylases that activate gene expression via demethylating H3K27me3 to H3K27me2 or H3K27me1 [91]. Inflammatory pathways involve the histone demethylase JMJD3 (also known as KDM6B), which is induced by LPS/TLR4 signalling and removes an inhibitory histone modification, H3K27me3 [92]. Pro-inflammatory TLR4 gene activation was decreased in JMJD3-deficient macrophages. In line with

these results, targeting JMJD3 H3K27me3 demethylases with small-molecule inhibitors impairs inflammatory responses in human primary macrophages and could thus be of high pharmacological interest for the treatment of inflammatory diseases including T2D [93]. The absence of JMJD3 completely blocks the induction of M2 macrophages in mice challenged with helminths or chitin, indicating that the role of JMJD3 is greater in M2 than in M1 macrophages [94]. Importantly, although there is some controversy in this regard, M2 macrophage polarisation in response to IL-4 seems to be largely independent of JMJD3. This indicates that the induction of M2 macrophages in response to alternative stimuli follows different routes. JMJD3 seems to function by controlling expression of IRF4, which in turn is required for M2 polarisation of macrophages [94]. Although this pathway is strongly supported by human genetics data, the molecular and mechanistic details are still unclear. Specifically, it is not known how inflammatory signals affect JMJD3 expression and function and how JMJD3 would be selectively recruited to gene promoters and enhancers, given its limited set of regulated genes. The dual role of JMJD3 in both M1 and M2 polarisation is not necessarily enigmatic and probably reflects the need for JMJD3 to enable responses to various environmental stimuli. Overall, JMJD3 actions are, in addition to HDAC3, another example for a chromatin modifier that integrates responses to different inflammatory stimuli at the epigenomic level, including IL-4, receptor activator of nuclear factor kappa B ligand, macrophage colony-stimulating factor, SAA, and LPS/TLR4 signalling. Epigenetic signatures differ in chronic inflammatory disease states such as T2D, and JMJD3 represents one of the few examples for an epigenetic modifier that could be directly involved in these alterations in macrophages. Gallager et al. revealed a potential new role for JMJD3 in modulating IL-12 expression by macrophages in the setting of T2D [95]. This is in agreement with a recent study where treatment of macrophages with a selective JMJD3 inhibitor led to alterations in pro-inflammatory cytokine [93]. However, it is not possible to determine the degree to which the observed changes in histone methylation are due to nutrient overconsumption and obesity, insulin resistance, or hyperglycaemia. A recent clinical study revealed that alterations in DNA methylation are predominantly the consequence of adiposity, rather than the cause [96]. The methylation loci identified genes involved in lipid and lipoprotein metabolism, substrate transport, and inflammatory pathways. Interestingly, this study also suggested that the disturbances in DNA methylation predict future development of T2D, which provides new insights into the biological pathways influenced by adiposity, and may enable development of new strategies for prediction and prevention of T2D and other adverse clinical consequences of obesity. In line with this report, JMJD3 seems to be a potential candidate for macrophage polarisation and the onset of T2D [97]. Further work is needed to investigate how changes in epigenetic signatures in metabolic diseases are controlled by JMJD3 and how these chromatin modifications are reversible upon JMJD3 inhibition.

Closing remarks and perspectives

Macrophages are major players in the pathogenesis and the progression of T2D. Understanding the regulatory circuits that govern their function is critical in combatting the disease. As reviewed, transcription factors and coregulators have a crucial function in the polarisation of macrophages (Table 1 and Fig. 1). Although research into transcriptional regulation of macrophages with regard to T2D has taken off in past decades, fundamental questions still remain unanswered. Molecular studies on defining the sensitive regulatory regions of inflammatory genes have revealed the importance the genomic regulatory regions called enhancer and super-enhancers. Despite that it is well admitted that the enhancers are of importance in macrophage lineage differentiation, their relevance/functionality in disease with inflammatory components, such as T2D, has to be proven. In our recent study, we demonstrated that the loss of GPS2's repressive function at the CCL2 enhancer regions provokes an uncontrolled induction of CCL2 when mice with a myeloid-specific GPS2 deficiency face metabolic stress [88]. Our study suggests novel concepts that propose inappropriate enhancer activity in macrophages (and particularly adipose tissue macrophage) may have pathological consequences at the tissue and systemic levels. Admittedly, the vast majority of experimental data (including our own data) reported is obtained from animal studies. In contrast, few studies have been performed in human macrophages in a T2D context. Most of the studies have analysed DNA methylation (probably because of the easiest manner to quantify epigenetic modification linked to human diseases) but these analyses can give only limited information regarding the active status of enhancers (when they can be identified). In fact, enhancer activity is mostly driven by histone modifications instead of DNA methylation. Effort in defining the repertoire of enhancers in macrophages in the context of T2D and its complications has to be carried out when considering T2D as an 'enhancer disease' as recently suggested in cancer. Since T2D and its complications are associated with genetic predisposition, we could ask whether genetic variants within or nearby enhancers may modify their accessibility or activity, a phenomenon that may accelerate the progression of disease due to an exacerbated inflammation. Recent studies performed in metabolic cells have confirmed this possibility. Indeed, mutation with PPAR response element limits PPAR action in adipocytes and favours obesity complications.

In contrast to type 1 diabetes (T1D) with a clear autoimmune aetiology, T2D is an inflammatory disease, with a relatively poor characterisation of the factors underpinning sterile

Table 1 Summary of the different mouse models studying factors implicated in macrophages polarisation in T2D

Mice models	Diabetic profile	Mechanisms	References
Global and myeloid specific IRF5 −/−	Anti-inflammatory phenotype ↑ Sensitivity ↑ Glucose tolerance ↓ Liver fibrosis upon NASH model	↑ M2 polarised adipose tissue macrophages ↑ Adipocyte size ↓ Inflammatory and apoptotic signalling in liver ↓ Hepatocyte death and scarring fibrogenesis	[39, 41]
Myeloid specific IRF4−/−	Pro-inflammatory phenotype ↓ Insulin signalling in adipose tissue, muscle, liver ↑ Insulin resistance on HFD	↑ Pro-inflammatory macrophages in adipose tissue ↑ Systemic inflammation	[42]
TLR2 antisense oligonucleotides	Antisense oligonucleotide Anti-inflammatory phenotype ↑ Improved insulin sensitivity and signalling in muscle, liver and WAT	Antisense oligonucleotide ↓ Activation of IKBKB, MAPK8 and phosphorylation of IRS1 model ↓ Inflammation/IL1B signalling	[98, 99]
TLR2−/−	KO Model Anti-inflammatory phenotype ↑ Glucose tolerance ↑ Insulin sensitivity ↑ Insulin secretion		
Global KO TLR4 bone marrow transplant with TLR4 −/− cells	↓ Inflammation = Macrophage accumulation in adipose tissue = Insulin sensitivity after HFD	↓ Inflammation ↓ Activation of IKBK	[40, 100]
Loss-of-function mutation in TLR4	Loss of function mutation ↓ Obesity on high-fat diet ↑ Insulin sensitivity and signalling (systemically and in adipose tissue, liver and muscle)	↓Inflammation ↓Activation of IKBK	
STAT3 Inhibitor in APOE−/− mice	Inhibitor in APOE Inflammation ↓ Monocyte-to-macrophage differentiation ↓ Monocyte infiltration into atherosclerotic plaques	AMPK-mediated inhibition of STAT3 activation	[18, 20]
Myeloid-specific JAK2 KO	↓ Myeloid-specific JAK2 KO ↓ Weight gain on HFD ↓ Insulin-resistance on HFD ↓ Inflammation ↓ Macrophage infiltration in adipose tissue (↓ CLS) ↓ Adipocyte size ↑ Adipogenesis	↓ Chemokine expression from peritoneal infiltrate ↓ STAT3 phosphorylation (specific to STAT3)	
STAT6 Global KO STAT6−/−	Global KO STAT6−/− ↓ Weight gain on HFD ↓ Fat mass on HFD ↓ Adipocyte size = Adipogenesis = Food intake ↑ Energy expenditure ↓ Glucose tolerance	↑ PPARα activity—fatty acid mobilisation and metabolism ↑ FGF21 expression (hepatic and circulating)	[21, 22]

Table 1 (continued)

Mice models	Diabetic profile	Mechanisms	References
	↓ Insulin signalling (p-AKT in liver, muscle, adipose tissue)		
VASP-deficient mice	Pro-inflammatory phenotype VASP−/− bone marrow transplantation: ↑ Liver inflammation ↑ Insulin resistance	↓ STAT6 phosphorylation in VASP−/− macrophages	
AP-1Global JNK1−/− and/or JNK2−/−	↓ Body weight on HFD ↑ Insulin sensitivity on HFD	↓ JNK activity and cytokine expression in the liver	[29, 31]
JNK −/−	↓ Body weight on HFD and ob/ob ↓ Adipocyte size on HFD and ob/ob ↑ Insulin sensitivity on HFD and ob/ob ↑ Insulin receptor signalling on HFD and ob/ob (liver, muscle and adipose tissue)	↓ JNK activity ↓ Inflammation ↑ Insulin receptor signalling on HFD and ob/ob (liver, muscle and adipose tissue)	
Myeloid-specific JNK−/− by bone marrow transplantation	= Body weight and adipocity ↑ Insulin sensitivity	↓ JNK activity ↓ Inflammation	
NF-κB			[101]
Hepatic IKKB−/−Myeloid IKKB−/−	↑ Insulin sensitivity in liver of hepatic IKKB−/− = Insulin resistance in other tissues	↓ NF-κB activity (local and systemic) ↓ Inflammation (local and systemic)	
HFD, obesity and ageing	↑ Insulin sensitivity in liver of myeloid IKKB−/− ↓ Global insulin resistance in myeloid IKKB−/−		
Myeloid specific PPAR- β/δ −/−	Pro-inflammatory phenotype, ↑ hepatic dysfunction ↑ systemic insulin resistance	Macrophages and kuppfer cells impaired alternative activation. ↓ Hepatic oxidative metabolism	[53, 102]
Myeloid specific PPAR-γ −/−	Pro-inflammatory phenotype, ↑ predisposition to diet-induced obesity, ↑ insulin resistance, ↑ glucose intolerance.	↓ M2 macrophages (impaired maturation and activation) with ↓ IL4, IL13 expression	[62]
Myeloid specific HIF1-α −/−	Protective anti-inflammatory phenotype ↑ Insulin sensitivity	↓ M1 macrophages and CLS ↓ Activation of pro-inflammatory and angiogenic genes	[80, 81]
Myeloid specific GPS2 −/−	Pro-inflammatory profile ↑ insulin resistance, ↑ glucose intolerance, pro-diabetogenic phenotype	Derepression of CCL2 and IL6 genes by derepressing of c-JUN	[88]
Myeloid specific NCoR−/−	Protective anti-inflammatory phenotype ↑ systemic insulin sensitivity upon HFD	Derepression of LXRs, ↑ genes involved in biosynthesis of palmitoleic acid and ω3 fatty acids Inhibition of NF-κB	[85]

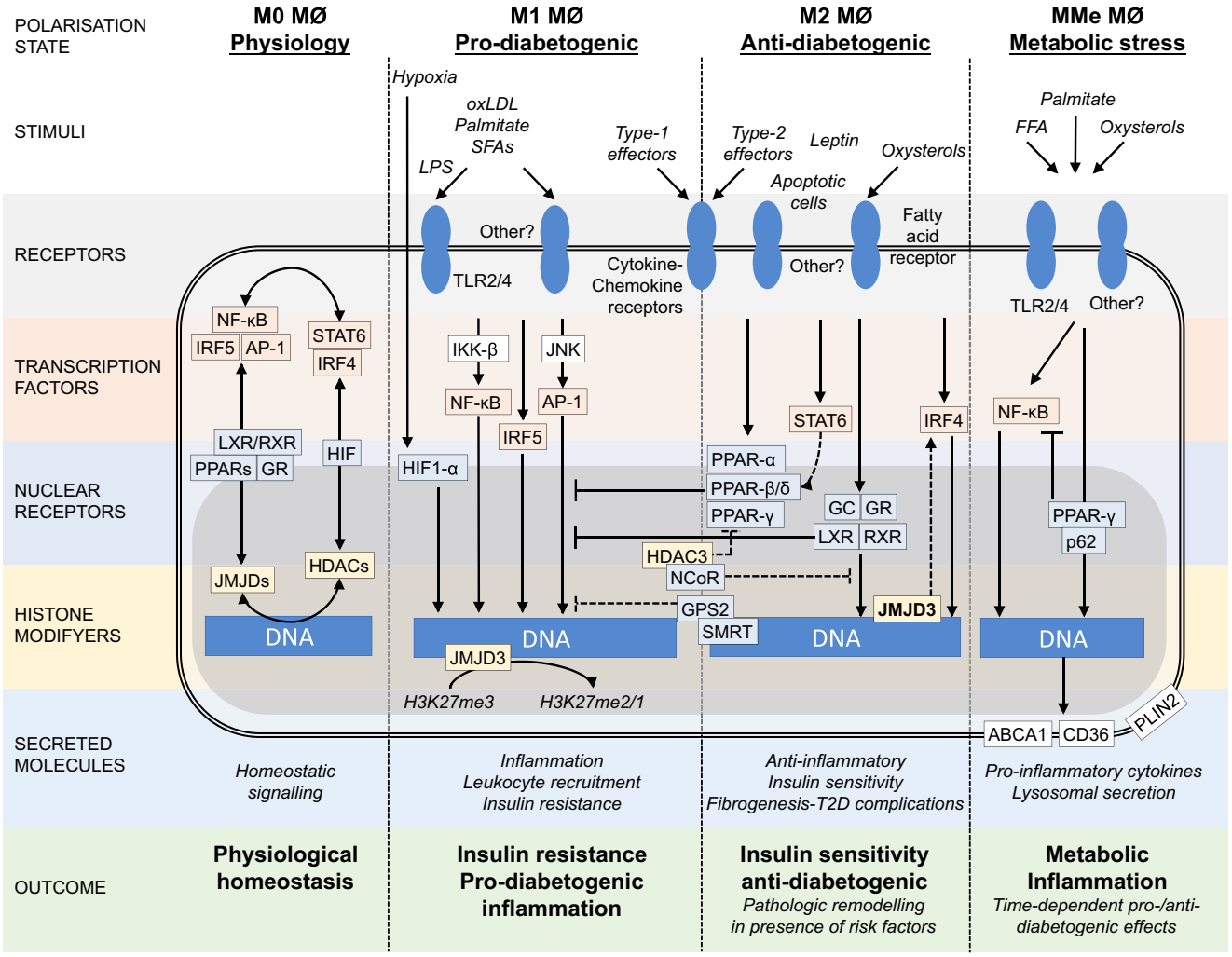

Fig. 1 Representing the different macrophage subclasses and their contribution to the progression of insulino-resistance and type 2 diabetes. It summarises the major transcriptional pathways involved in macrophages polarisation (i.e. M1, M2 and MMe) and the outcome of this activation status at the systemic and tissue levels

inflammation. Recent research has turned its attention toward risk, notably the factors leading up to the inflammatory activation of macrophages. Immunometabolic studies have shown that alterations in the metabolic profile of macrophages shape their activation state and function. Leading candidates in T2D are glucose, lipids (cholesterols, ceramides, lipolysis products), advanced glycation end-products (AGEs) and damage-associated molecular patterns (DAMPs; e.g. products of necrosis). SFA activation of TLR4 is the most attractive mechanism of inflammation in T2D, conveniently linking obesity to inflammation and insulin resistance. Importantly, lipid intermediates are very well known ligands for nuclear receptors such as fatty acids and oxysterols for PPARs and LXRs respectively. Additionally, metabolite intermediates such acetyl-CoA and alpha-ketoglutarate are co-factors of epigenomic modifiers like HDACs and KDMs. Thus, metabolic reprogramming of macrophages could become a therapeutic approach to limit disease progression in conditions that where macrophages are a leading component, such as T2D. In this light, exciting new studies have turned their attention to the ways in which macrophages handle their own metabolism, physiologically and under pathologic circumstances. Notably, studies on IRF5 have shown that genetic variants that lead to its over-expression also contribute to increased rates of glycolysis in macrophages [103]. This relationship between glycolysis and pro-inflammatory function has previously been established; however, the novelty represented by this study is in the repurposing of canonically inflammatory transcription factors into metabolic transcription factors. Granted these studies have been carried out in the context of genetic gain-of-function risk variants and with the mechanistic use of known TLR ligands (LPS in this case), they are nonetheless extremely relevant and merit greater attention. A regulatory link between pro-inflammatory machinery that also adapts cellular metabolism can explain much of how metabolic intermediates are created within immune cells to provide positive or

negative feedback loops to coregulators and histone modifiers, later tempering the inflammatory response under physiological circumstances. Future targeting of such intricate cell autonomous regulatory cascades will certainly add valuable insight to current knowledge of the multiple levels of regulation and promise to widen the range of actionable therapeutic targets in both inflammatory and metabolic conditions. Importantly, widening the field of investigation to other tissues important in diabetic pathogenesis is essential, namely pancreatic beta cells. Macrophages, amongst other immune cells, have been identified in the beta cells; however, literature is scarce with regard to the transcriptional control of their activation (see review in this same issue by E. Dalmas). Future work should focus on their physiological and pathological roles and importantly on the transcriptional mechanisms of their differentiation.

Funding information N.V. was supported by grants from the French National Agency of Research (AngioSafe and PROVIDE), Region Ile de France (CORDDIM), Paris City (EMERGENCE), French and European Foundations for Diabetes (SFD and EFSD) and the European Union H2020 framework (ERC-EpiFAT).

Compliance with ethical standards

Conflict of interest The authors declare no competing financial interests.

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