REVIEW

Recent insight into the correlation of SREBP-mediated lipid metabolism and innate immune response

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Abstract

Fatty acids are essential nutrients that contribute to several intracellular functions. Fatty acid synthesis and oxidation are known to be regulated by sterol regulatory element-binding proteins (SREBPs), which play a pivotal role in the regulation of cellular triglyceride synthesis and cholesterol biogenesis. Recent studies point to a multifunctional role of SREBPs in the pathogenesis of metabolic diseases, such as obesity, type II diabetes and cancer as well as in immune responses. Notably, fatty acid metabolic intermediates are involved in energy homeostasis and pathophysiological conditions. In particular, intracellular fatty acid metabolism affects an inflammatory response, thereby influencing metabolic diseases. The objective of this review is to summarize the recent advances in our understanding of the dual role of SREBPs in both lipid metabolism and inflammation-mediated metabolic diseases.

Key Words

- ▶ SREBP
- ▶ lipid metabolism
- ▶ inflammation
- ▶ innate immune response

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Introduction

Modern-day dietary habits, featuring high fat and high carbohydrate intake, have triggered global health problems (Popkin *et al.* 2012). Undoubtedly, these dietary trends have resulted in an epidemic of metabolic diseases that has led to an increase in the number of people living with serious metabolic dysfunctions (e.g., diabetes) as well as cardiovascular diseases (Monteiro & Azevedo 2010, Han & Lean 2016).

Cellular lipids and cholesterol are important for the maintenance of a steady-state level of membrane biosynthesis and coordinate many biological processes, such as cell growth and metabolic homeostasis (Muro *et al.* 2014, Shimano & Sato 2017). Cellular triglyceride homeostasis and cholesterol metabolism are regulated by sterol regulatory element-binding proteins (SREBPs) (Brown & Goldstein 1997). SREBPs are synthesized in

a precursor form. For activation, the complex of SREBP with SREBP cleavage-activating protein (SCAP) dissociates from insulin-induced genes and relocates from the endoplasmic reticulum (ER) to the Golgi apparatus, where SREBPs are sequentially cleaved by site 1 (S1P) and site 2 (S2P) proteases (Daemen *et al.* 2013). The nuclear form of SREBP enters the nucleus to act as a transcription factor (Shimano & Sato 2017). The SREBP family contains SREBP-1a, SREBP-1c and SREBP-2. SREBP-1c is the predominant isoform expressed in the liver, whereas *Srebp-1a* is highly expressed in cells of the immune system, such as bone marrow-derived macrophages and dendritic cells (Im *et al.* 2011). *Srebp-2* is ubiquitously present in various tissues (Hua *et al.* 1993). Although there is some functional overlap among SREBP isoforms, SREBP-1a and SREBP-1c are involved in fatty acid (FA) metabolism,

such as the FA and triacylglycerol (TG) biosynthesis pathways, whereas SREBP-2 is the master regulator of cholesterol synthesis and lipogenesis (Daemen *et al.* 2013, Xu *et al.* 2013b).

Recent studies have expanded the list of known functions of SREBP-1 to include systemic biological processes for cellular lipid homeostasis (Jeon & Osborne 2012). The objective of this review is to summarize the recent advances in our understanding of the functions of SREBP-1 as a bridge between metabolism and the immune system in mammals.

Recent insights into immunometabolism

Recently, research on immunometabolism, the interplay between immunological and metabolic processes, revealed that specific metabolic activities are required for proper immune-cell differentiation and function (O'Neill *et al.* 2016). Cellular metabolism is important for facilitating the functions of immune cells. Nutrients not only are fuels for metabolic pathways but are also involved in modulating the activity of important regulators of immune metabolism and function (Loftus & Finlay 2015). In T cells, for example, glutamine deprivation compromises activation-induced T cell growth and proliferation, and HIF1 and MYC are induced upon T cell activation (Wang *et al.* 2011), whereas the induction of glutamine uptake and metabolism requires extracellular signal regulated kinase (ERK) function, driving T cell activation (Carr *et al.* 2010). Glucose metabolism and mTORC1-HIF1 α signaling are required for neutrophil effector functions like the formation of neutrophil extracellular traps (McInturff *et al.* 2012).

Metabolic enzymes can have a direct role in the control over immune responses. In myeloid cells, glyceraldehyde 3-phosphate dehydrogenase (GAPDH) involved in glycolysis is a component of the interferon γ -activated inhibitor of translation (GAIT) complex, which binds defined elements in the 3' untranslated region (UTR) within the family of inflammatory mRNAs and suppresses their translation (Mukhopadhyay *et al.* 2009). In addition, immune stimuli can cause reprogramming of metabolic pathways. Activation of macrophages with lipopolysaccharide (LPS) disrupts the Krebs cycle, resulting in accumulation of succinate and HIF1 α activation, promoting induction of IL-1 β transcription (Tannahill *et al.* 2013). LPS enhances glycolysis where enzyme hexokinase 1 primes the NLRP3 inflammasome to stimulate pro-IL-1 β processing (Moon *et al.* 2015). Moreover, immune cells can reprogram their cellular

metabolism under the influence of significant metabolic stressors caused by altered microenvironments and function in immunity. Altered glutamine metabolism, e.g., glutamine deprivation or inhibition of N-glycosylation, decreases M2 polarization of macrophages (Jha *et al.* 2015). Glycolysis is needed for the functioning of Th17 cells as inflammatory lymphocytes; when glycolysis is blocked in T cells, they become regulatory T cells serving as anti-inflammatory regulators (Buck *et al.* 2015).

Immune cells with different functions use distinct metabolic pathways to ensure energy homeostasis and to control molecular biosynthesis for growth and proliferation (Loftus & Finlay 2015). As one example, activated lymphocytes after stimulation through antigen or cytokine receptors maintain aerobic glycolysis increasing the rates of both glycolysis and oxidative phosphorylation, but mature myeloid cells tend to be non-proliferative and thus employ aerobic glycolysis (Loftus & Finlay 2015).

Many studies have successfully shown connections among metabolism, immunity and inflammation at the intracellular level (Ertunc & Hotamisligil 2016, Buck *et al.* 2017). Early immunometabolism studies described the metabolic demands for the function of immune cells (Oren *et al.* 1963, Newsholme *et al.* 1986). One research group demonstrated that the main inflammatory signaling pathway, which involves nuclear factor κ B (NF- κ B) and the inhibitor of κ B kinase β (IKK β), is stimulated in obesity and insulin resistance (Shoelson *et al.* 2003). In addition, it was revealed that c-Jun N-terminal protein kinases (JNKs) are activated as pro-inflammatory factors during obesity-related inflammation (Hirosumi *et al.* 2002). Collectively, these findings highlight the tight connection of metabolism and inflammation, giving rise to an entirely new field of biomedical research referred to as immunometabolism (Mraz & Haluzik 2014).

The relation between lipids and inflammation

Lipids play pivotal roles in metabolism, immunity and cancer as inflammatory mediators. Indeed, cholesterol, FAs and modified lipids can directly activate inflammatory pathways. Adipokines are also involved in inflammatory processes (Asrih & Jornayvaz 2013). Production of most adipokines is upregulated in the obese state, and these pro-inflammatory proteins typically function to promote obesity-associated metabolic diseases. TNF α and IL-6 are among the more recently identified adipokines including resistin, retinol-binding protein 4 (RBP4), lipocalin 2 (LCN2), IL-18, angiopoietin-like protein 2 (ANGPTL2),

CC-chemokine ligand 2 (CCL2), CXC-chemokine ligand 5 (CXCL5) and nicotinamide phosphoribosyltransferase (NAMPT) (Ouchi *et al.* 2011). Leptin is an adipokine synthesized primarily by the white adipose tissue, but also expressed in the immune cells that exert relevant actions both on metabolism and the immune system (Abella *et al.* 2017). Leptin participates in innate immunity by inhibiting natural killer (NK) cells immune functions and NK cells proliferation (Wrann *et al.* 2012) and increasing the expression of monocyte surface markers (Conde *et al.* 2010). Leptin is involved in the adaptive immune system by enhancing proliferation and responsiveness of regulatory T cells (De Rosa *et al.* 2007) and by activating B cells to induce secretion of IL-6, IL-10 and TNF α (Agrawal *et al.* 2011). Moreover, leptin exerts its pro-inflammatory and pro-catabolic actions on cartilage and triggers degeneration of articular cartilage, which is characteristic of osteoarthritis (Dumond *et al.* 2003). In addition to the numerous pro-inflammatory adipokines described earlier, adipose tissues secrete a few anti-inflammatory factors, such as adiponectin and SFRP5, which were recently identified as adipokines (Ouchi *et al.* 2003, Berg & Scherer 2005, Ouchi *et al.* 2010). Adiponectin levels in plasma and adipose tissue are lower in obese individuals compared with lean individuals (Ryo *et al.* 2004). Consistent with decreased adiponectin level in obesity, the production of adiponectin in adipocytes is inhibited by pro-inflammatory factors, such as TNF α and IL-6, as well as by hypoxia and oxidative stress (Hosogai *et al.* 2007).

The liver is an important metabolic organ that responds to energy imbalances and performs a key function in lipid homeostasis (Canbay *et al.* 2007). Ectopic fat accumulation in the liver and the subsequent hepatic insulin resistance cause either local inflammation mediated by the liver or systematic inflammation mediated by white adipose tissue (WAT) (Asrih & Jornayvaz 2013). Previously, WAT has been regarded as a static storage site for excess energy or as a material for thermal and mechanical insulation of the body. Nonetheless, WAT has emerged as a dynamic tissue for the integration of metabolic, endocrine and immune functions that participates in whole-body homeostasis, which is maintained by an orchestrated interplay of immune cells and chemical signals (Mraz & Haluzik 2014, Maurizi *et al.* 2018).

In macrophages, lipid metabolism can trigger inflammation. Studies in hyperlipidemic mouse models suggest that high circulating levels of chylomicrons, very low-density lipoprotein and their remnants induce hepatic inflammation via enhanced scavenger

receptor-mediated uptake of these lipoproteins by Kupffer cells (KCs; i.e., liver tissue-resident macrophages), thereby triggering an inflammatory response in the liver (van Diepen *et al.* 2013). In addition, macrophage-specific genetic ablation of a fatty acid-binding protein (FABP4, also known as aP2) suppresses inflammatory signaling and attenuates activation of the NF- κ B pathway (Xu *et al.* 2015). Furthermore, KCs are involved in an important mechanism underlying nonalcoholic fatty liver disease (NAFLD) (Smith 2013, Wan *et al.* 2014). In the early stages of the disease, KC population expands rapidly, and KCs secrete cytokines and chemokines such as IL-1 β , TNF α , CCL2 and CCL5, contributing to paracrine activation of protective or apoptotic signaling pathways in hepatocytes and to the recruitment of other immune cells (Dixon *et al.* 2013). In the KCs of rats with NAFLD, liver X receptor α (LXR α), SREBP-1c and fatty acid synthase (FAS) mRNA and protein levels are elevated, indicating that high-fat diet (HFD)-induced high LXR α levels may increase *Fas* expression through activation of the SREBP-1c pathway (Gong *et al.* 2014). In obesity, during an HFD, KCs are polarized to M1 activation (which represents pro-inflammatory macrophages) and are reported to augment hepatic inflammation and consequently accelerate hepatic steatosis (McArdle *et al.* 2013). KCs are responsive not only to inflammatory signals but also to metabolic fluctuations. As mentioned earlier, lipids *per se* and high-energy diets can be harmful to the liver. Evidence shows that an overload of lipids and cholesterol derivatives activates KCs in the fatty liver disease and steatohepatitis (Dixon *et al.* 2013). *In vitro* stimulation of mouse KCs with saturated fatty acids (SFAs) upregulates toll-like receptors (TLRs) (Tang *et al.* 2013). Thus, free FA sensing by KCs may condition their responsiveness to pro-inflammatory triggers.

It is well known that FAs are transported to various organs including the liver and skeletal muscle under physiological conditions; thereafter, FAs are broken down through β -oxidation in the mitochondria or are stored as TGs (Rambold *et al.* 2015). Notably, stored hepatic TGs predominantly originate from the lipolysis of TGs released from WAT. Dietary FAs and *de novo* lipogenesis are the major sources of other lipid stores (Asrih & Jornayvaz 2013, Saponaro *et al.* 2015). Imbalances between complex pathways lead to excessive FA flux and accumulation. Downstream products, including fatty acyl-coenzyme A, diacylglycerol and ceramides, mediate the lipotoxic effects, resulting in several metabolic diseases, e.g., obesity and diabetes (Jornayvaz & Shulman 2012, Asrih & Jornayvaz 2013). Indeed, these pathology-related

lipid species have been shown to interfere with signaling via modulation of serine/threonine kinases, such as protein kinase C, JNK, IKK and the mechanistic target of rapamycin (mTOR), thus indicating lipid-induced insulin resistance and promoting inflammation, apoptosis and hypertrophy (Ritchie *et al.* 2017).

FAs have also been shown to modulate T cell function and specific functions of innate and acquired immunity (De Jong *et al.* 2014, Whelan *et al.* 2016). High levels of n-3 poly unsaturated fatty acids (PUFAs) to healthy animals or human subjects results in suppression of the ability of lymphocytes to respond to mitogen stimulation, NK cell activity and delayed type hypersensitivity reactions (Kew *et al.* 2004). Immunomodulatory effects of n-3 PUFA enhance eicosanoid formation, signal transduction, gene expression and lipid peroxidation. Long-chain n-3 PUFAs, such as eicosapentaenoic and docosahexaenoic acids (EPA and DHA) influence proliferation, maturation and differentiation of lymphocytes through decrease of diacylglyceride and ceramide levels and decrease of *IL-2* mRNA expression and secretion. Since n-3 PUFA antagonizes the stimulation of inflammatory response, there is potential for benefit in asthma and chronic inflammatory diseases (Calder 2010). The pathogenesis of NAFLD is known to involve inflammatory signaling pathways such as NF- κ B/IKK β , JNK and mitogen-activated protein kinase (MAPK) cascades (Yang *et al.* 2012, Zeng *et al.* 2014).

FA oxidation and FA synthesis have different roles in the immune system. FA oxidation is associated with the differentiation of macrophages toward the anti-inflammatory M2 phenotype and formation of inflammation-suppressing regulatory T cells, which subsequently increase the expression of FA oxidation-related genes, including carnitine O-palmitoyltransferase 1 alpha (CPT1a). Constitutively active CPT1a increases FA oxidation and reduces the production of inflammatory cytokines and lipid accumulation (Patsoukis *et al.* 2015, O'Neill *et al.* 2016). On the other hand, FA synthesis is related to the formation and function of pro-inflammatory immune cells. Several studies show that enhanced FA synthesis in macrophages is triggered by inflammatory stimuli (Calder 2010, Ecker *et al.* 2010, Kelly & O'Neill 2015). In addition, the cytokines being made by Th17 cells depend on the type of FA being synthesized. For example, production of IL-10, an anti-inflammatory cytokine, is promoted when polyunsaturated FAs are present but is limited when SFAs are present. In other words, SFAs and polyunsaturated FAs lead to opposite inflammatory responses through recognition by distinct

receptors. SFAs trigger a pro-inflammatory response through TLR4 receptor, and polyunsaturated FAs engage G protein-coupled receptor 120 (GPR120) to induce an anti-inflammatory signaling cascade (Osborn *et al.* 2012). At the same time, lipid metabolism disorders are mediated by the LXR α /SREBP-1c signaling pathway in liver tissue during NAFLD (He *et al.* 2011, Xu *et al.* 2013a). Because FAs substantially participate in the development of NAFLD, targeting of lipid synthesis is considered a therapeutic strategy to prevent hepatic steatosis (Asrih & Jornayvaz 2013).

FA and cholesterol homeostasis are tightly controlled at the level of transcription by LXRs and SREBPs (Oishi *et al.* 2017). Both sterols and oxysterols reconsidered for their fundamental activity as ligands of SREBP and LXR are elevated in metabolic disorders and influence immune cell function (Cagno *et al.* 2017). Oxysterols are a family of cholesterol oxidation and derivative mainly 25-hydroxycholesterol (25-HC), 27-hydroxycholesterol (27-HC) and 24-hydroxycholesterol (24-HC). In non-alcoholic steatohepatitis, 27-HC reduces accumulation of cholesterol in lysosomes of KCs to promote an anti-inflammatory phenotype (Bieghs *et al.* 2013, Hendriks *et al.* 2015). Elevations in 27-HC via deletion of cytochrome P450 family 27 subfamily B polypeptide 1 (CYP7B1), which functioned in the metabolism of cholesterol metabolites, such as 27-HC promote atherosclerosis in apoE-deficient atherosclerotic mouse model (Umetani *et al.* 2014). Similarly, in monocyte/macrophages 27-HC negatively impacts bone homeostasis via activation of LXR, which inhibits osteoblast differentiation and increases the TNF α expression (Nelson *et al.* 2011).

Srebp-1a and *Lxra* are highly expressed in macrophages and known regulators of cytokine release from macrophages (Joseph *et al.* 2004, Worby & Dixon 2011). *Srebp-1* KO macrophages exhibited reduced production of anti-inflammatory FAs (Hien *et al.* 2017). In other reports, bacterial alpha-toxin-induced SREBP-1a activates lipogenesis and the anti-apoptotic factor *Api6* gene following bacterial infection of macrophages, which provides protection from apoptosis induced by bacterial toxins (Tie *et al.* 2012). Similar late hyper-inflammatory trends were observed in *Srebp-1* KO macrophages stimulated with ligands for TLR2 and TLR3. Therefore, *Srebp-1* is genetically required for the normal resolution phase in macrophages (Hien *et al.* 2017). LPS treatment increases SREBP-1a activity and *de novo* synthesis of cholesteryl esters and triglycerides in peritoneal macrophages (Posokhova *et al.* 2008). Consistent with these findings, LPS challenges in *Srebp-1a*-deficient bone

marrow-derived macrophages are protected against LPS-induced IL-1 β production (Im *et al.* 2011). Im *et al.* showed that SREBP-1a required for the expression of the inflammasome components inducing the cleavage of inflammatory cytokines pro-IL-1 β and pro-IL-18, which are necessary for the production of mature cytokines and secretion of IL-1 β in response to systemic inflammation such as endotoxic shock (Franchi *et al.* 2009, Im *et al.* 2011). These findings indicate that SREBP activation is linked to an M1 phenotype in macrophages (Hubler & Kennedy 2016). Given the importance of SREBP in mediating inflammation, it is not surprising that SREBPs have evolved as 'metabolic integrators' that effectively bridge broader physiological processes with basic intermediary lipid metabolism (Kloet *et al.* 2012).

SREBPs are major transcription factors that regulate cellular lipid metabolism and homeostasis (Horton *et al.* 2002). During fasting, *Srebp-1c* expression is low in the liver but dramatically increases after feeding; this increase is mediated by insulin (Xu *et al.* 2013b). In states of energy abundance, protein kinase B (AKT)-mTOR-SREBP signaling increases lipogenesis (Asrih & Jornayvaz 2013). Lipid-mediated cellular stress (lipotoxicity) caused by SREBP-1 activation contributes to metabolic diseases such as obesity, diabetes mellitus, dyslipidemia and hepatosteatosis, thereby aggravating SREBP-related pathology such as inflammation and fibrosis (Fig. 1) (Shimano & Sato 2017).

In many studies, researchers have tried to link lipid metabolism to an immune response. For instance, GPR40

and GPR120, which are members of the G protein-coupled receptor (GPCR) family, are involved in anti-inflammatory processes in macrophages, and currently, there is emerging interest in their metabolic effects. These receptors are associated with obesity, insulin responses and subsequent inflammation (Agrawal *et al.* 2017). According to studies on human subjects, fasting insulin and glucose levels are linked to protein tyrosine phosphatase receptor J (PTPRJ), which is a regulator of T cell signaling (Manning *et al.* 2012), and the variant of ST6GAL1 involved in antigen production is associated with susceptibility to type 2 diabetes mellitus (Kooner *et al.* 2011). Nonetheless, so far, the exact mechanism and function of SREBPs in the immune system remain to be discovered.

SREBP-1a and SREBP-2 are known to play an important role in phagocytosis by promoting membrane biogenesis to compensate for the loss of the plasma membrane when the cell engulfs particles, such as bacteria (Shao & Espenshade 2012). Notably, *Srebp-1a* is highly expressed in immune cells and is involved in the activation of a lipogenic gene, such as FAS, acetyl-CoA carboxylase (ACC) and stearoyl-CoA desaturase-1 (SCD-1), and nucleotide-binding oligomerisation domain, leucine-rich repeat proteins 1a (NLRP1a), a core inflammasome component (Im *et al.* 2011). Moreover, a recent study revealed that SREBP-1 promotes TLR4-induced gene activation and reprograms macrophage lipid metabolism, including biosynthesis of anti-inflammatory FAs, resulting in the resolution of inflammatory responses (Oishi *et al.* 2017). Nevertheless, SREBP-1c enhances the nonesterified-fatty acid-induced

Figure 1

Regulation of metabolic diseases through inflammation by SREBP.

overactivation of the NF- κ B inflammatory pathway by increasing production of reactive oxygen species. This signaling is not promoted through TLR4, which triggers further hepatic inflammatory damage in dairy cows with fatty liver (Li *et al.* 2015). In addition, hepatic steatosis and activation of the hepatic IKK α /NF- κ B inflammatory pathways are observed in *Srebp-1c*-overexpressing mice (Li *et al.* 2015). In HFD-induced NAFLD animal model, both sulfated oxysterol and 5-cholesten-3 β -25-diol 3-sulfate (25HC3S) reduce lipid accumulation in serum and liver and also suppress lipid-induced inflammation in the liver. Therefore, 25HC3S may be a potent endogenous regulator that suppresses the SREBP-1c signaling pathway (Xu *et al.* 2013a).

SREBPs perform broader functions in cell metabolism and act as regulators of essential lipid homeostasis (Desvergne *et al.* 2006, Daemen *et al.* 2013). On the other hand, SREBPs are regulated by diverse mechanisms in different tissues (Goldstein *et al.* 2006, Shao & Espenshade 2012). As mentioned earlier, recent studies revealed more varied roles for SREBPs in lipid metabolism and in immune responses (Oishi *et al.* 2017). Some studies have raised several questions about the participation of SREBPs in immunometabolism, fibrometabolism and mitochondrial function; about the relation between endogenous or exogenous FAs and cholesterol and about the role of nutrients and metabolites in the regulation of SREBP-1 maturation.

Conclusions

Future studies will focus on deepening our molecular understanding of the immune-metabolic cross-talk. Interventions targeting key molecules in these immune-metabolic interactions may be utilized to modify immune contributions to metabolic diseases. An understanding of the immune-metabolic cross-talk at the molecular level may shed light on the forces that determine immune and metabolic homeostasis and the pathogenesis of immune-system-mediated or -associated metabolic diseases.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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