Journal of Autoimmunity 104 (2019) 102335

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Autoimmune epithelitis (Sjögren's syndrome); the impact of metabolic status of glandular epithelial cells on auto-immunogenicity

Stergios Katsiougiannis[a,*], Roxane Tenta[a], Fotini N. Skopouli[a,b]

[a] Department of Nutrition and Clinical Dietetics, Harokopio University, Athens, Greece El. Venizelou 70, Athens, 17671, Greece
[b] Euroclinic of Athens, Department of Internal Medicine and Autoimmune Diseases, Athanasiadou 7-9, Athens, 11521, Greece

A B S T R A C T

It is well established that distinct cell metabolic alterations strongly contribute to the modulation of innate and adaptive immune responses. In the past decade the term immunometabolism has been introduced to describe the intracellular metabolic shifts of immune cells that lead to alterations of their functions. The pathogenesis of Sjögren's syndrome (SS), also referred to as autoimmune epithelitis, is not completely understood, but strong evidence supports the central role of the salivary glandular epithelial cells which are the target cells in the initiation of the autoimmune responses. Moreover, the altered epithelial functional phenotype, observed in the salivary gland lesion, may explain their disturbed secretory as well as immunoregulatory functions. From an immunometabolic perspective we have focused our studies on the endoplasmic reticulum (ER) of the salivary gland epithelial cells (SGEC) and the implication of its altered functions in the immunogenicity of these cells in SS. We showed that ER of SGEC in SS patients *in situ* is stressed and extensively dilated. Using salivary gland cell cultures, we studied *in vitro* the effect of ER stress on the metabolic behavior and viability of the cells. ER stress induced by thapsigargin increased spliced X-box binding protein-1 (XBP-1, transcription factor that increases the transcription of UPR target genes) levels in a time-dependent manner followed by autophagy and resulted to cell apoptosis. In apoptotic cells, we observed that the autoantigens Ro52 and La were redistributed in apoptotic blebs. During the induction of ER stress autophagy rescued the cells from apoptosis acting as a protective mechanism. We have also shown that adiponectin, a multifunctional hormone, is upregulated in the SGEC of SS patients acting in an autocrine or paracrine manner in the same cells. Adiponectin through activation of AMPK, the major sensor for cell energy demands, protected SGEC from apoptosis. Our results in combination with the work of others indicate that any effort of cell adaptation to ER stress may up regulate a proinflammatory milieu. This enhances the notion that metabolic alterations of the targeted epithelial cells in SS, independently of the cause, may induce an immunogenic phenotype. Therefore, SGEC have the potential to directly regulate susceptibility to and/or severity of autoimmune responses. Since adiponectin plays a vital role in the viability of SGEC through phosphorylation of AMPK, therapeutic interventions using PPAR agonists that upregulate adiponectin and concomitantly modify the energy metabolism, may be promising candidates for therapeutic intervention in SS.

1. Introduction

The initiators of autoantibodies production as well as the immune cell-mediated tissue injury are key research questions in the field of autoimmune diseases. The auto-aggression of the immune response, evident once clinical manifestations become apparent, initially made it difficult to conceptualize that an apparently uncontrolled attack on self could be initiated by the target tissue itself. Notably, in some

Abbreviations: SS, Sjögren's syndrome; ER, Endoplasmic Reticulum; SGEC, Salivary Gland Epithelial Cells; XBP-1, X-box binding protein-1; AMPK, 5′ adenosine monophosphate-activated protein kinase; PPAR, peroxisome proliferator-activated receptors; TCR, T-cell receptor; OXPHOS, Oxidative phosphorylation; Teff, effector T cells; Treg, T regulatory cells; mTORC1, mammalian target of rapamycin complex 1; GRP78/BiP, 78 kDa glucose-regulated protein; UPR, Unfolded Protein Response; ERdj, ER-localized DnaJ proteins; ATP, Adenosine triphosphate; TEM, transmission electron microscopy; LSG, Labial Salivary Gland; ATF6α, Activating transcription factor 6 α; STING, stimulator of interferon genes; LC3, microtubule-associated protein 1 light chain 3; 3-MA, 3-Methyladenine; TG, thapsigargin; HSG, human submandibular gland cell line; IRF, Interferon regulatory factor; IFN, Interferon; IL-6, Interleukin-6; IL-4, Interleukin-4; MHC, Major histocompatibility complex; NOD, non-obese diabetic mice; TNF-α, Tumor Necrosis Factor α

* Corresponding author. Department of Nutrition and Clinical Dietetics, Harokopio University 70 El. Venizelou, Athens, 17671, Greece.
E-mail address: sakats@hua.gr (S. Katsiougiannis).

https://doi.org/10.1016/j.jaut.2019.102335
Received 4 September 2019; Accepted 9 September 2019
Available online 18 September 2019

autoimmune diseases, such as Sjogren's syndrome (SS), evidence supports that the main targets, the epithelial cells of the salivary glands might be able to initiate autoimmune responses by provoking/triggering the immune cells through aberrant expression of several proinflammatory molecules and neoantigens [1–6]. The pathophysiological mechanism of this aberrant phenotype able to initiate autoimmune response remains elusive.

In recent years, the emergence of immunometabolism as a key concept in the regulation of immune responses provides a new dimension to our understanding of the role of metabolic conditions in immune functions in health and disease [7,8]. It is now well recognized that intracellular metabolic pathways are important regulators of immune differentiation and activation, and thus directly influence the immune responses including autoimmune reactivity [9].

In an attempt to gain a better understanding of the role of target cells in SS, our group has generated data revealing the importance of salivary gland cells' metabolic signature in auto-antigenicity, as indicated by the occurrence of endoplasmic reticulum stress, autophagy, immunogenic apoptosis and upregulation of adiponectin [10–12].

2. Immunometabolism is a novel perspective in immunology

In the past ten years a substantial number of discoveries have been made in the field of immunometabolism, by which is meant the intracellular metabolic shifts in immune cells, that leads to alterations of their functions. Cellular metabolism instructs and modulates immune cell differentiation and function in physiology and disease [7]. It is now well established that for immune cells in order to execute their specialized functions they should engage anabolic metabolism [8]. In the absence of a TCR signal, naïve T cells have reduced surface expression of nutrient transporters [13], maintaining a catabolic state that involves autophagy, OXPHOS and fatty acid oxidation [14]. A "shift" from OXPHOS to aerobic glycolysis is the hallmark of T cell activation [15]. As T cells differentiate their metabolic demands change and this is best illustrated by Teff and T regulatory (Treg) cells. Teff cells rely primarily on glucose to support their functions [15] while FOXP3-expressing Treg cells have decreased requirements for glycolysis [16]. Similarly, the secretion of antibodies by B lymphocytes is an energetically demanding response. In fact, B lymphocytes undergo metabolic rewiring involving the energy-regulating kinase complex mTORC1 and mitochondrial remodeling, necessary to mount effective antibody production [17–19].

Consistent with the above, metabolic alterations in the intracellular levels of specific metabolites are linked to the inflammatory phenotype of immune cells which are implicated in various autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and diabetes [9,20]. Various organelles, such as endoplasmic reticulum (ER) and mitochondria are pivotal regulators of cell's metabolism and compelling evidence suggests that ER stress exerts profound effects on several central metabolic processes [21,22], placing ER on the frontier of immunometabolism research.

The translational importance of metabolism in regulating immunity is further supported by recent works showing that targeting central metabolic components such as AMP-activated protein kinase, mTOR and hexokinase ameliorates autoimmune inflammation by metformin [23,24] rapamycin [25] and 2-deoxy-D-glucose respectively [26,27]. In fact, it has been shown that inhibition of metabolic pathways in experimental models of systemic lupus erythematosus has profound effects without any apparent toxicity [26]. Therefore, cellular metabolism is a highly adaptive driver for cellular fate decisions and critical immune regulator under physiological and pathological conditions such as autoimmune diseases.

3. Sjogren's syndrome: cross talk between targeted tissues and immune cells

Sjogren's syndrome is a systemic autoimmune disease in which the target of the autoimmune attack are exocrine gland tissues, mainly the lachrymal and salivary glands. Clinical and pathology studies have shown that the autoreactive immunocytes surround and attack epithelial cells not only of the exocrine glands but also around bronchial and renal epithelia and cholangia. These milestone observations directed Dr. Moutsopoulos in the early 90s to introduce the term "Autoimmune epithelitis" for the syndrome [28]. Subsequent tissue immunopathology and salivary gland epithelial cell cultures studies revealed that these cells are activated since they inappropriately express immunoreactive molecules [5,29–31], release exosomes containing autoantigens [32] and have the ability to act as antigen presenting cells. These observations suggested that these cells are the initiators and perpetuators of autoimmune reactivity [1]. In other words, it appears that the epithelia, non-immune cells, play a major role in the autoimmune arena.

Since metabolic aberrations of immune cells drive immune regulation in mammals, it was postulated that the "immune" phenotype of SGEC, undergoes similar control by their metabolism and may actively shape the autoimmune response in SS. On this basis, our group initiated a research program asking whether and to what extend target cells' metabolic status has a role in the immunogenic phenotype. To address this, we investigated the possible involvement of metabolic regulatory mechanisms in salivary gland epithelium of patients with SS that may affect the specific auto-immunogenicity of the disease.

4. Endoplasmic reticulum: demand for energy

A common characteristic of secretory cells is the extended ER. The acinar and ductal cells of salivary glands belong to the cells with the most extended ER and they are metabolically active cells, since continuously produce saliva, a fluid rich in proteins. Extended ER is also present in other secretory cells, against which the immune system is acting in SS, such as epithelial cells of the lachrymal glands, bronchioles, cholangia and renal tubules.

The ER system has many different cellular functions including synthesis, folding, modification and transport of proteins, as well as storage of calcium [33]. The production and the secretion of the salivary proteins depend on the physiological ER function and the Ca^{2+} homeostasis in ductal and acinar salivary cells [34–36]. However, when a protracted stimulus triggers the cells to produce increased amount of protein, disturb the calcium homeostasis [37], interfere with the necessary energy amount for these processes and the ER system is stressed.

Like other professional secretory cells that synthesize large amounts of proteins (e.g., plasma cells, hepatocytes, or pancreatic exocrine cells), SGEC are estimated to secrete an immense amount of proteins per second [38,39]. This feature is achieved not only by having an elaborate ER machinery that contains an abundance of protein-folding network but also by maintaining a sophisticated system to recognize and discard misfolded proteins when are accumulated. Protein folding in the ER is a highly complex process that is dependent on a multitude of factors. In fact, it is estimated that in the average cell, one third of all proteins produced in the ER are misfolded under homeostatic conditions [40], implying that even greater rates of protein misfolding might occur when cells are either injured or under stressed conditions. To cope with these interactions, cells possess high levels of chaperone proteins in their ER lumen, which function to physically block misfolded or unfolded proteins [40,41]. GRP78/BiP is one of the most important ER chaperone proteins playing a major role in chaperoning newly synthesized proteins [42]. GRP78/BiP is responsible for targeting misfolded proteins for retrograde translocation towards the proteasome for degradation, and sensing conditions of ER stress to activate the mammalian unfolded protein response (UPR). The binding of adenosine nucleotides by GRP78/BiP has a vital role in these activities and its interaction with specific ER-localized DnaJ (ERdj) family proteins allows it to achieve several cellular functions [42]. Importantly, the activities of chaperone proteins are dependent on the hydrolysis of ATP;

thus, they require a constant supply of energy to perform their vital functions. This energy dependence likely explains why ER stress is often observed in cells deprived of essential nutrients or has significant metabolic impairments [43].

5. Endoplasmic reticulum in SS

The cellular responses to ER stress are multifaceted and include the activation of a series of signaling pathways such as UPR, autophagy and cell death. The UPR system is an energy-consuming process requiring ATP and upon its activation cells eliminate their biosynthetic program in order to save energy and support it [44]. Given the requirement for ATP in chaperone function, the initiation and maintenance of the UPR are likely to be influenced by cellular energy levels. Several observations are consistent with the need for adequate energy to sustain ER function. This metabolic support, necessary for the proper chaperon protein synthesis and function is one of the most critical metabolic adaptations to ER stress. In mammalian cells it has been shown that UPR activation leads to the transcriptional upregulation of a number of autophagy-related genes [45,46]. Autophagy, as a catabolic process allows cells to reutilize their own constituents for energy and eventually provides the stressed cells with the necessary biomolecules for chaperone synthesis and efficient UPR function. These events are activated in order to relieve stress and restore ER homeostasis. However, prolonged or unresolved ER stress results in apoptotic cell death [47].

In a very recent work from our group, to investigate the status of ER in SS we assessed its subcellular morphology using transmission electron microscopy (TEM) in minor salivary gland biopsies of patients and control individuals. The analysis of TEM images revealed extensive dilation of the ER cisternae in salivary gland epithelial cells derived from SS donors compared to controls ([48] and unpublished data). ER lumen dilation is a definitive marker of ER stress and this finding is particularly important and reveals that a major organelle of the target tissue in SS is severely disturbed.

These *in situ* findings directed us to further assess ER stress in cultured primary SGEC from SS and control donors. Using GRP78/Bip and Xbp-1 as markers for UPR activation and in line with the previous findings, our *in vitro* data demonstrate that: 1) SGEC derived from SS patients appear to sustain the increased ER stress phenotype under long term culture and 2) ER stress is a rather endogenous characteristic of diseased SGEC phenotype than transiently induced by the microenvironment, further supporting the potential role of target cells in the initiation of the autoimmune response in SS ([48] and unpublished data). In addition, Barrera et al. have shown Increased ATF6α pathway activation in LSG from SS-patients [49]. ATF6α is a major component of ER stress and these data, although obtained by using whole LSG tissue samples that include different cell types, provides additional support on our findings that SGEC are ER stressed.

In another recent work it was shown that the chaperone protein ERdj5 is highly expressed in the minor salivary glands of SS patients, with stain intensity correlating to inflammatory lesion severity and *anti*-SSA/Ro positivity [50]. Moreover, it was demonstrated higher Xbp-1 activation within the salivary glands of SS patients. These observations provide a clear picture of the stressed ER machinery in salivary glands of SS patients and further support the existence of aberrant phenotype in target tissue before the autoimmune response is initiated. The above-mentioned studies of ER disturbancies in SS are depicted in Table 1.

Remarkably, in an animal model of ER stress, ablation of the chaperone protein ERdj5 develop many of the central features of SS, like spontaneous inflammation of salivary gland with infiltrating T and B lymphocytes, distinct cytokine signature, excessive cell death, reduced saliva flow, and production of *anti*-SSA/Ro and *anti*-SSB/La autoantibodies. Notably, these features were more pronounced in female mice [50].

Several molecules downstream of the ER stress machinery, which can be activated by metabolic stress, are recognized as potential inducers of inflammatory and immune response. ER stress-induced molecules particularly relevant to SS are: the IRF family transcription factors activation and IL-6 production by the stressed cells during UPR activation [51–53], the surface MHC expression on the cells that facilitate the antigen presentation during autophagy process [47] and the ribonucleoprotein exposure to the surface of the cells within the apoptotic blebs [12].

Table 1
Studies revealing disturbances of ER in Sjogren's syndrome.

ER disturbance	Species/Tissue	Ref.
Dilation of ER cisternae	Human SGEC *in situ*	[48]
Increased GRP78/Bip	Human SGEC *in situ* & culture	[48,50]
Increased Xbp-1	Human SGEC culture	[48,50]
Increased ERdj5	Human SGEC *in situ*	[50]
Increased ATF6α	Human LSG	[49]
SS-like disease induced by ERdj5 ablation	ERdj5$^{-/-}$ mouse	[50]
ER stress-induced autophagy	Human HSG cells	[12]
ER stress-induced apoptosis	Human HSG cells	[12]
ER stress-induced redistribution of Ro/SSA and La/SSB in apoptotic blebs	Human HSG cells	[12]

Viruses contribute to ER stress in salivary gland epithelial cells and this is particularly supported by the interferon signature in minor salivary glands of SS patients [54]. It has been described that ER stress significantly augments type I interferon immune response in the setting of pathogen challenge, such as viral infection [55]. Nevertheless, it has been described that oxygen-glucose deprivation and pharmacologic UPR inducers, activate IRF3 in the absence of pattern recognition stimulation [56]. Recently, activation of energy sensors such as AMPK have been linked to modulation of the stimulator of interferon genes (STING) signaling [57]. STING is located in the ER membrane and appears to play a critical role in the induction of type 1 IFNs. Finally, chronic stress is thought to be an important inducer of ER stress response in salivary glands. Preliminary data from our ongoing experiments appear to confirm this novel hypothesis in the context of SS pathogenesis ([48] and unpublished data).

6. Autophagy links ER stress to immunogenic apoptosis

Autophagy is an evolutionarily-conserved and genetically-regulated pathway that recycles cellular content and controls the intracellular turnover of proteins, organelles, and pathogens through the initiation of lysosome-dependent degradation system. Degradation of cytoplasmic content in turn generates metabolites necessary for anabolic processes, such as cell growth and proliferation as well as the remodeling that occurs during differentiation of immune cells. In fulfilling these capacities, autophagy is a fundamental mechanism for the maintenance of metabolic homeostasis under normal and pathological conditions [58].

When autophagy degrades cytoplasmic content, the resulting metabolite products directly feed into cellular metabolic pathways, thus intimately linking autophagy with metabolism. Autophagy metabolites are then used for energy generation or for biomolecules synthesis. Notably, autophagic proteolysis results in free amino acids which can directly feed into central metabolism. Concurrently, by degrading lipid droplets (lipophagy) [59] or mitochondria (mitophagy) [60] autophagy has the capability to interfere and redirect cellular metabolite flow. Finally, autophagy is controlled and regulated by two key sensors for energy and nutrient availability, namely AMPK and MTOR [61–63] further substantiating that cellular energy-metabolic balance, autophagy, and their regulation via AMPK and mTOR signaling are intimately linked.

To investigate the involvement of autophagy in target salivary gland epithelial cells we tested its role in cell death after induction of ER stress. First, we asked whether a conventional ER stress inducer elicits autophagy. HSG cells were treated with the ER stressor thapsigargin

Table 2
Pharmaceutical targeting of PPARs in autoimmune diseases.

Pharmaceutical molecule	Disease	Targeted PPAR	Experimental model	Effect	Ref.
Rosiglitazone Ciglitazone	SS	PPARγ	Human SGEC	Anti-inflammatory Anti-apoptotic	[75]
Rosiglitazone	SS	PPARγ	NOD mice	Amelioration of histopathologic lesion Decreased IL-6, TNF-alpha Increased IL-4	[76]
Pioglitazone + methotrexate	Rheumatoid arthritis	PPARγ	Wistar albino rats	Suppression of disease activity	[77]
Rosiglitazone	Scleroderma	PPARγ	Skin scleroderma fibroblasts	Alleviation of fibrotic phenotype	[78]
Pioglitazone	Type 1 diabetes	PPARγ	NOD mice	Induction of UPR, improved β-cell function	[82]
Troglitazone Rosiglitazone	Experimental colitis	PPARγ	Swiss-Webster mice	Lower disease activity index	[80]

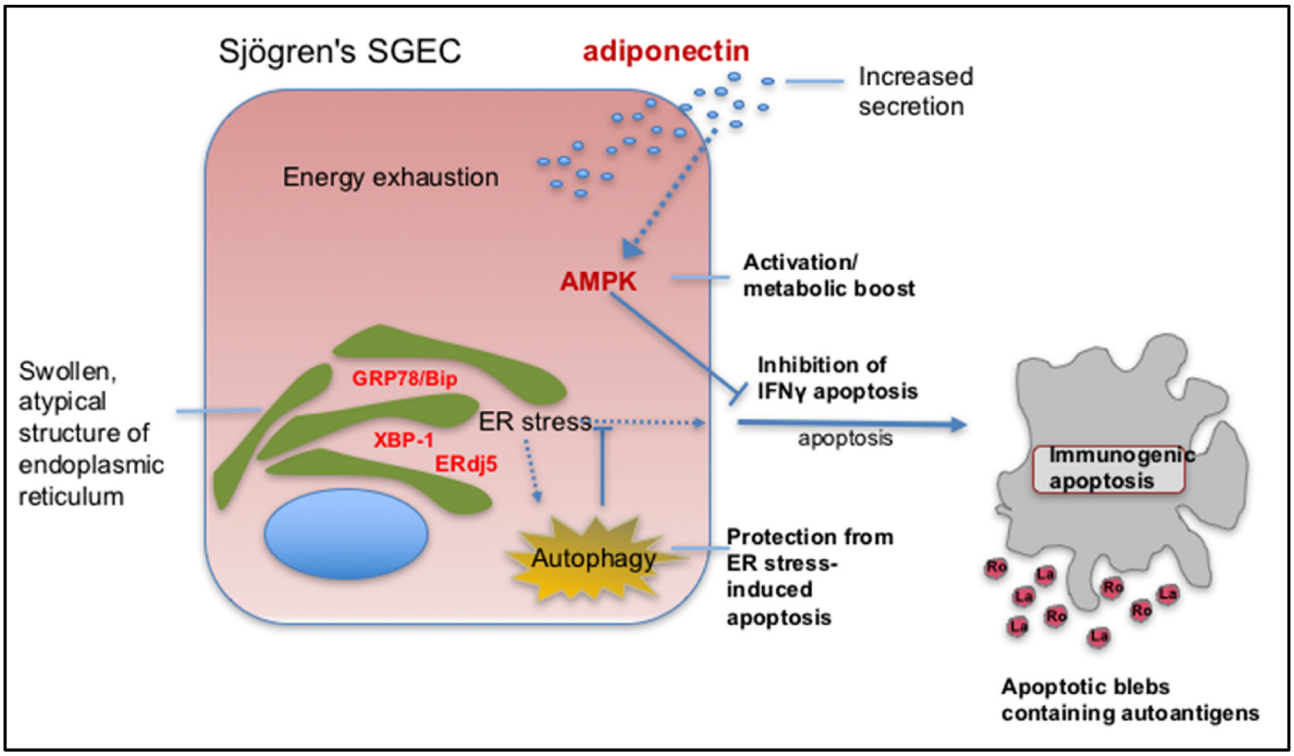

Fig. 1. Schematic representation of documented metabolic alterations of SGEC in SS.

Table 3
Key questions in the study of metabolism in salivary epithelium of SS.

- What is the energy status of SGEC in SS?
- Which are the major organelles involved in SGEC energetics?
- How does energy supply or deprivation affect the immune phenotype of SGEC?
- How does metabolism regulate epigenetic changes during the course of SS?
- How the autoantigens to commonly autoantibodies, observed in SS, are implicated in the altered metabolic process of SGEC.
- Is it possible to target specific events in immunometabolism of SGEC and achieve a therapeutic effect in SS?

(TG). The conversion of the cytoplasmic form of microtubule-associated protein 1 light chain 3 (LC3-I) to the membrane-bound form (LC3-II) reflects the number of autophagosomes formed, and this is indicative of autophagy induction. After triggering ER stress with TG, LC3-I was converted to LC3-II in a time-dependent manner indicating the induction of autophagy in salivary gland cells. Later on, after prolonged ER stress (24 h) autophagy was attenuated, which may reflect the induction of cell death under constant ER stress conditions [12].

To gain a deeper understanding of the role of autophagy in ER-induced cell death we used the autophagy inhibitor 3-MA, an inhibitor of the class III phosphoinositide 3-kinase. HSG cells were subjected to the ER stress (TG) in the presence or absence of 3-MA. Treatment of HSG with 3-MA increased tremendously the percentage of ER stress-induced apoptosis. Autophagy inhibition alone did not affect the apoptotic process and did not produce additional damage to TG-treated cells [12]. These data clearly indicate that autophagy might partially compensate for a stressed ER, since an active autophagic machinery is protective during ER stress-induced cell death.

Traditionally, during programmed cell death, mainly in the form of apoptosis, intracellular content is confined within membranous vesicles called apoptotic bodies, that are rapidly been up taken by phagocytes in an immunologically “silent” manner. For this reason, apoptosis has long been considered a non-immunogenic or even tolerogenic process [64,65]. However, based on newer data, apoptosis is no longer considered to be an immunologically “silent” process, since apoptotic cells are able to induce antigen-specific immune responses [66]. This new concept of “immunogenic cell death” has challenged the traditional view and has granted apoptosis with immunogenic abilities. This immunostimulatory type of apoptosis is characterized mainly by the ability of dying cells to release damage-associated molecular patterns (DAMPS) or autoantigens, resulting in the induction of robust immune responses against self-antigens [67]. Hence, immunogenic cell death is thought to be a significant mechanism in the initiation of autoimmune response. In particular, for SS, apoptosis of salivary gland epithelial cells has been shown to elicit the activation of self-reactive lymphocytes in an animal model [68].

In our studies we sought to investigate the possible effect of ER stress on immunogenic apoptosis by following the cellular distribution of the two major autoantigens of SS, Ro52/SSA and La/SSB. These autoantigens are expressed in a relatively diffuse cytoplasmic pattern in the normal HSG cells with low and partial staining of the nucleus. When we induced ER stress on HSG cells, both Ro52/SSA and La/SSB showed a striking pattern of re-localization during different stages of apoptosis. In cells at a relatively early stage of apoptosis after ER stress, a reduced cytoplasmic staining of the two autoantigens was observed. Ro52/SSA and La/SSB were re-localized to the periphery forming thin eccentric rims or crescents inside the cell membrane. At the final stages of apoptosis, where HSG cells were in the process of forming apoptotic blebs, Ro52/SSA and La/SSB were abundantly found in these blebs [12]. The fact that intracellular autoantigens such as Ro52/SSA and La/SSB can be exposed to the immune system through apoptotic blebs could represent a typical form of immunogenic apoptosis in the salivary gland lesion of SS. Thus, immunogenic apoptosis of glandular epithelial cells may be one of the critical contributors in autoimmune responses in SS.

Collectively, our studies suggest that a metabolic shift of salivary gland cells such as induction of autophagy might be of significant importance in maintaining cell viability. When autophagy is blocked, salivary gland cells undergo apoptotic death which might be immunostimulatory since the two major autoantigens of the disease are exposed to the immune cells. Future studies in SS should delineate the potential benefits of targeting autophagy machinery and boosting metabolic pathways against immunogenic cell fate.

7. Metabolic adaptation of the target tissue: the importance of adiponectin and AMPK

Adiponectin is one of the most studied hormones with metabolic and immunoregulatory properties. There is ample evidence supporting its homeostatic function, which is mediated both by direct actions on metabolic cells and indirectly through immunomodulatory effects on immune cells [69].

At the time, adiponectin was thought to be an adipocyte-specific hormone and in 2006 our work demonstrated for the first time the production of adiponectin by SGEC, both *in situ* and in culture [10]. When we compared the levels of adiponectin expression between SS and controls we found that SGEC from patients with SS produce higher levels of adiponectin as shown by immunohistochemistry using salivary gland tissue biopsies. The higher constitutive secretion of adiponectin was further confirmed *in vitro* using SGEC derived from SS patients and controls. These findings led to the logical, yet intriguing question: why do the target cells in SS differentially produce and secrete a metabolic hormone? To answer that, adiponectin's biological role was tested in primary SGEC and it was initially shown that this hormone functions as a protective factor against spontaneous apoptosis. Since IFN-γ is a major proinflammatory cytokine in the microenvironment of SS lesions, adiponectin's protective function was further tested in the context of IFN-γ-induced cell death. The data showed that adiponectin confers anti-apoptotic protection against IFN-γ-induced cell death. Mechanistically, our experiments documented that adiponectin acts as a protective agent in SGEC by activating AMP-activated protein kinase (AMPK), the energy sensor of the cells [11]. AMPK is a critical sensor in cellular energy homeostasis. When AMPK is phosphorylated a series of anabolic pathways are initiated aiming to provide the necessary conditions for energy production and cell survival. The data suggest that the target SGEC in SS become resistant to apoptosis induced by IFN-γ by secreting adiponectin which acts in an autocrine and/or paracrine manner. When a specific inhibitor was used to block AMPK phosphorylation by adiponectin, SGEC became vulnerable to IFN-γ-induced apoptosis [11]. The central role of AMPK in this process highlights the importance of cell metabolism in target cell survival and uncovers a previously unknown mechanism in the salivary lesion of SS. This finding provides a potential pathway through which AMPK may regulate cell survival under energy stress conditions such as autoimmune inflammation and substantiates the intimate connection between energy metabolism and inflammation.

8. Pharmaceutical products used for metabolic diseases; are they a reasonable therapeutic intervention for autoimmunity?

The labial glandular epithelial cells in SS appear with a metabolically imbalanced phenotype where ER is one of the major contributors. The expression of adiponectin could be interpreted as a “biomarker”, indicating the constant regulation of the epithelial cell's metabolic needs for the maintenance its basic functions and survival [11,70,71]. Thus, adiponectin represents a key molecule and a potential target for therapeutic intervention. Adiponectin is up-regulated by insulin sensitizers such as glitazones, metformin, sulfonylurea and resveratrol [72] as well as by lipid lowering drugs such as fibrates [73]. Both glitazones and fibrates act through receptors which are called peroxisome proliferator activated receptors (PPARs).

PPARs are a family of nuclear receptors, of which three major isoforms have been identified (α, β/δ, and γ) [74]. The receptor isoforms display tissue and cell specificity and upon activation wield interrelated but distinct functions. PPARγ has been the best characterized, due to their insulin sensitizing and glucose metabolism stabilizing effects. Agonists of the PPARγ are currently used for treatment of type 2 diabetes. More recently some of these same agonists were shown to exert anti-inflammatory and anti-proliferative effects. PPAR-alpha is a transcription factor and a major regulator of lipid metabolism. PPAR-alpha is activated under energy deprivation status and is essential for ketogenesis, a significant adaptive response to prolonged starvation.

The anti-inflammatory action of glitazones has raised the interest of scientists to study their effects in experimental animal models as well as in patients with autoimmune diseases and dissect their mechanism of action as therapeutic tools for autoimmune diseases. Recently a comparative analysis of LSG biopsies and salivary gland epithelial cells (SGEC) obtained from SS patients and controls had revealed that PPARγ receptors are strongly expressed in the ductal epithelia of normal salivary glands while constitutively reduced in ductal epithelial cells of SS patients [75]. The induction of PPARγ activity by synthetic ligands in salivary gland epithelial cell lines was shown to have a potent intracellular anti-inflammatory effect, demonstrated by the down-regulation of various immuno-active molecules expression, as well as of NF-κB and IL-1β activity. The reduced epithelial PPARγ signaling in SS patients was shown to correlate with the existence of constitutively active IL1-β and NF-κB pathways and this may largely contribute to unrestrained epithelial activation [75].

A few years ago Li et al. [76], investigated the anti-inflammatory effect of PPAR-γ on non-obese diabetic mice (NOD mice), which develop some of the central phenotypic characteristics of Sjogren's syndrome. Mice were randomly divided into 2 groups and rosiglitazone and normal saline were administered in the PPAR-γ group and the control group respectively. The levels of IL-1β, IL-6 and TNF-α were gradually increased in PPAR-γ group and controls and the level of IL-4 was gradually increased in PPAR-γ group. At the age of 18 weeks, the levels of IL-6 and TNF-α were significantly lower and the level of IL-4 was significantly higher in the serum of PPAR-γ group treated with rosiglitazone compared to control group.

The research approaches and therapeutic interventions using PPAR agonists in the above studies in SS experimental animal models were generally focused on their anti-inflammatory action. However, the role of PPAR agonists in enhancing energy supply of the cell, which may be decisively involved in the anti-inflammatory action, has never been investigated. A deeper understanding of the downstream molecular cascade under various energy conditions will open new directions for therapeutic approaches.

Ongoing clinical studies are further investigating the effects of several PPAR-targeting compounds in the treatment of various

inflammatory disorders such as rheumatoid arthritis scleroderma and inflammatory bowel disease [77–80]. However, despite the progress in molecular pharmacology, SS still remains a disorder without an effective therapeutic modality. Biologic agents have been proven ineffective, particularly the *anti*-TNFs, for amelioration of disease symptoms and progression [81]. The PPARγ agonists due to their *in vitro* and *in situ* anti-inflammatory effects and their therapeutic efficacy in NOD mice [76,82] represent a promising therapeutic agent for SS. The fact that these agents are already in the market and their side effects are well known, make them very attractive as candidates for testing of their safety and effectiveness in SS patients. Table 2 summarizes the findings of studies using PPAR agonists in autoimmune diseases.

9. Conclusions and outlook

Although the exact pathogenic mechanisms underlying the heterogeneous autoimmune responses in SS are not known, epithelial cells appear to play a key role. They are suitably equipped to drive and regulate immune responses by actively interacting with the immune cells and driving their activation, accumulation and differentiation.

We present and discuss here evidence suggesting that SGEC metabolism and immune phenotype may be interconnected more than previously anticipated and may actually reflect different steps of a common signaling axis that can determine their strategic role in the initiation of the local lesions in SS.

SGEC are secretory cells with constant high energy demands and their metabolic machinery is expected to suit their life-style. Disturbances of this process may be enforced by insufficient energy supply, ER stress or even chronic stress, leading to metabolic reprogramming and eventually immunogenic cell death characterized by the release of cellular autoantigens in the form of apoptotic blebs. Differential adiponectin production by SGEC in SS indicates a low energy phenotype and the antiapoptotic effects of adiponectin mediated by phosphorylation of AMPK provide a robust paradigm for the interconnection between metabolism and immune functions of SGEC in the context of glandular lesion in SS. Fig. 1 provides a visual summary of these phenomena.

The identification of the causes for the SS-associated epithelial activation and the unraveling of the interactions between metabolism and immune phenotype are of great importance for the understanding of disease pathogenesis and the development of newer effective therapeutic strategies. Hence, we can expect broader findings in this burgeoning field. Table 3 describes key questions which might guide us to a more comprehensive approach of glandular lesions in SS putting immunometabolism at the forefront of our investigations.

Conflicts of interest

The authors declare no conflicts of interest with the contents of this article.

Acknowledgements

This project has been funded in part by the European Union's Horizon 2020 multicentric protocol HARMONICSS; H2020-SC1-2016; GA#: 731944.

References

[1] H.M. Moutsopoulos, Sjogren's syndrome: a forty-year scientific journey, J. Autoimmun. 51 (2014) 1–9.
[2] D. Boumba, F.N. Skopouli, H.M. Moutsopoulos, Cytokine mRNA expression in the labial salivary gland tissues from patients with primary Sjogren's syndrome, Br. J. Rheumatol. 34 (1995) 326–333.
[3] R.I. Fox, H.I. Kang, D. Ando, J. Abrams, E. Pisa, Cytokine mRNA expression in salivary gland biopsies of Sjogren's syndrome, J. Immunol. 152 (1994) 5532–5539.
[4] E.K. Kapsogeorgou, H.M. Moutsopoulos, M.N. Manoussakis, Functional expression of a costimulatory B7.2 (CD86) protein on human salivary gland epithelial cells that interacts with the CD28 receptor, but has reduced binding to CTLA4, J. Immunol. 166 (2001) 3107–3113.
[5] M.P. Spachidou, E. Bourazopoulou, C.I. Maratheftis, E.K. Kapsogeorgou, H.M. Moutsopoulos, A.G. Tzioufas, et al., Expression of functional Toll-like receptors by salivary gland epithelial cells: increased mRNA expression in cells derived from patients with primary Sjogren's syndrome, Clin. Exp. Immunol. 147 (2007) 497–503.
[6] A.G. Tzioufas, E.K. Kapsogeorgou, H.M. Moutsopoulos, Pathogenesis of Sjogren's syndrome: what we know and what we should learn, J. Autoimmun. 39 (2012) 4–8.
[7] L.A. O'Neill, R.J. Kishton, J. Rathmell, A guide to immunometabolism for immunologists, Nat. Rev. Immunol. 16 (2016) 553–565.
[8] E.L. Pearce, M.C. Poffenberger, C.H. Chang, R.G. Jones, Fueling immunity: insights into metabolism and lymphocyte function, Science 342 (2013) 1242454.
[9] L. Morel, Immunometabolism in systemic lupus erythematosus, Nat. Rev. Rheumatol. 13 (2017) 280–290.
[10] S. Katsiougiannis, E.K. Kapsogeorgou, M.N. Manoussakis, F.N. Skopouli, Salivary gland epithelial cells: a new source of the immunoregulatory hormone adiponectin, Arthritis Rheum. 54 (2006) 2295–2299.
[11] S. Katsiougiannis, R. Tenta, F.N. Skopouli, Activation of AMP-activated protein kinase by adiponectin rescues salivary gland epithelial cells from spontaneous and interferon-gamma-induced apoptosis, Arthritis Rheum. 62 (2010) 414–419.
[12] S. Katsiougiannis, R. Tenta, F.N. Skopouli, Endoplasmic reticulum stress causes autophagy and apoptosis leading to cellular redistribution of the autoantigens Ro/Sjogren's syndrome-related antigen A (SSA) and La/SSB in salivary gland epithelial cells, Clin. Exp. Immunol. 181 (2015) 244–252.
[13] J.C. Rathmell, M.G. Vander Heiden, M.H. Harris, K.A. Frauwirth, C.B. Thompson, The absence of extrinsic signals, nutrient utilization by lymphocytes is insufficient to maintain either cell size or viability, Mol. Cell 6 (2000) 683–692.
[14] C.J. Fox, P.S. Hammerman, C.B. Thompson, Fuel feeds function: energy metabolism and the T-cell response, Nat. Rev. Immunol. 5 (2005) 844–852.
[15] C.H. Chang, J.D. Curtis, L.B. Maggi Jr., B. Faubert, A.V. Villarino, D. O'Sullivan, et al., Posttranscriptional control of T cell effector function by aerobic glycolysis, Cell 153 (2013) 1239–1251.
[16] Z. Hu, Q. Zou, B. Su, Regulation of T cell immunity by cellular metabolism, Front. Med. 12 (2018) 463–472.
[17] A.L. Raybuck, S.H. Cho, J. Li, M.C. Rogers, K. Lee, C.L. Williams, et al., B cell-intrinsic mTORC1 promotes germinal center-defining transcription factor gene expression, somatic hypermutation, and memory B cell generation in humoral immunity, J. Immunol. 200 (2018) 2627–2639.
[18] L.R. Waters, F.M. Ahsan, D.M. Wolf, O. Shirihai, M.A. Teitell, Initial B cell activation induces metabolic reprogramming and mitochondrial remodeling, iScience 5 (2018) 99–109.
[19] A. Caro-Maldonado, R. Wang, A.G. Nichols, M. Kuraoka, S. Milasta, L.D. Sun, et al., Metabolic reprogramming is required for antibody production that is suppressed in anergic but exaggerated in chronically BAFF-exposed B cells, J. Immunol. 192 (2014) 3626–3636.
[20] J. Freitag, L. Berod, T. Kamradt, T. Sparwasser, Immunometabolism and autoimmunity, Immunol. Cell Biol. 94 (2016) 925–934.
[21] G.S. Hotamisligil, Endoplasmic reticulum stress and the inflammatory basis of metabolic disease, Cell 140 (2010) 900–917.
[22] U. Ozcan, Q. Cao, E. Yilmaz, A.H. Lee, N.N. Iwakoshi, E. Ozdelen, et al., Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes, Science 306 (2004) 457–461.
[23] H.J. Son, J. Lee, S.Y. Lee, E.K. Kim, M.J. Park, K.W. Kim, et al., Metformin attenuates experimental autoimmune arthritis through reciprocal regulation of Th17/Treg balance and osteoclastogenesis, Mediat. Inflamm. 2014 (2014) 973986.
[24] N. Nath, M. Khan, M.K. Paintlia, I. Singh, M.N. Hoda, S. Giri, Metformin attenuated the autoimmune disease of the central nervous system in animal models of multiple sclerosis, J. Immunol. 182 (2009) 8005–8014.
[25] Z. Li, L. Nie, L. Chen, Y. Sun, G. Li, Rapamycin relieves inflammation of experimental autoimmune encephalomyelitis by altering the balance of Treg/Th17 in a mouse model, Neurosci. Lett. 705 (2019) 39–45.
[26] S.C. Choi, A.A. Titov, G. Abboud, H.R. Seay, T.M. Brusko, D.C. Roopenian, et al., Inhibition of glucose metabolism selectively targets autoreactive follicular helper T cells, Nat. Commun. 9 (2018) 4369.
[27] Y. Yin, S.C. Choi, Z. Xu, L. Zeumer, N. Kanda, B.P. Croker, et al., Glucose oxidation is critical for CD4+ T cell activation in a mouse model of systemic lupus erythematosus, J. Immunol. 196 (2016) 80–90.
[28] H.M. Moutsopoulos, Sjogren's syndrome: autoimmune epithelitis, Clin. Immunol. Immunopathol. 72 (1994) 162–165.
[29] I.D. Dimitriou, E.K. Kapsogeorgou, H.M. Moutsopoulos, M.N. Manoussakis, CD40 on salivary gland epithelial cells: high constitutive expression by cultured cells from Sjogren's syndrome patients indicating their intrinsic activation, Clin. Exp. Immunol. 127 (2002) 386–392.
[30] M.N. Manoussakis, I.D. Dimitriou, E.K. Kapsogeorgou, G. Xanthou, S. Paikos, M. Polihronis, et al., Expression of B7 costimulatory molecules by salivary gland epithelial cells in patients with Sjogren's syndrome, Arthritis Rheum. 42 (1999) 229–239.
[31] E. Bourazopoulou, E.K. Kapsogeorgou, J.G. Routsias, M.N. Manoussakis, H.M. Moutsopoulos, A.G. Tzioufas, Functional expression of the alpha 2-macroglobulin receptor CD91 in salivary gland epithelial cells, J. Autoimmun. 33 (2009) 141–146.
[32] E.K. Kapsogeorgou, R.F. Abu-Helu, H.M. Moutsopoulos, M.N. Manoussakis, Salivary gland epithelial cell exosomes: a source of autoantigenic ribonucleoproteins, Arthritis Rheum. 52 (2005) 1517–1521.

[33] D.S. Schwarz, M.D. Blower, The endoplasmic reticulum: structure, function and response to cellular signaling, Cell. Mol. Life Sci. 73 (2016) 79–94.
[34] J.E. Melvin, D. Yule, T. Shuttleworth, T. Begenisich, Regulation of fluid and electrolyte secretion in salivary gland acinar cells, Annu. Rev. Physiol. 67 (2005) 445–469.
[35] I.S. Ambudkar, Polarization of calcium signaling and fluid secretion in salivary gland cells, Curr. Med. Chem. 19 (2012) 5774–5781.
[36] P. Sukumaran, Y. Sun, F.Q. Zangbede, V.N. da Conceicao, B. Mishra, B.B. Singh, TRPC1 expression and function inhibit ER stress and cell death in salivary gland cells, FASEB Bioadv. 1 (2019) 40–50.
[37] X. Liu, K.T. Cheng, B.C. Bandyopadhyay, B. Pani, A. Dietrich, B.C. Paria, et al., Attenuation of store-operated Ca2+ current impairs salivary gland fluid secretion in TRPC1(-/-) mice, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 17542–17547.
[38] J. Wu, R.J. Kaufman, From acute ER stress to physiological roles of the Unfolded Protein Response, Cell Death Differ. 13 (2006) 374–384.
[39] C. Mullins, The Biogenesis of Cellular Organelles, Landes Bioscience/Eurekah.com ; Kluwer Academic/Plenum, Georgetown, Tex. New York, N.Y., 2005.
[40] A.L. Fink, Chaperone-mediated protein folding, Physiol. Rev. 79 (1999) 425–449.
[41] T. Gidalevitz, F. Stevens, Y. Argon, Orchestration of secretory protein folding by ER chaperones, Biochim. Biophys. Acta 1833 (2013) 2410–2424.
[42] K.F.R. Pobre, G.J. Poet, L.M. Hendershot, The endoplasmic reticulum (ER) chaperone BiP is a master regulator of ER functions: getting by with a little help from ERdj friends, J. Biol. Chem. 294 (2019) 2098–2108.
[43] D. Ron, H.P. Harding, Protein-folding homeostasis in the endoplasmic reticulum and nutritional regulation, Cold Spring Harb. Perspect. Biol. 4 (2012).
[44] R. Bravo, V. Parra, D. Gatica, A.E. Rodriguez, N. Torrealba, F. Paredes, et al., Endoplasmic reticulum and the unfolded protein response: dynamics and metabolic integration, Int. Rev. Cell Mol. Biol. 301 (2013) 215–290.
[45] S. Deegan, S. Saveljeva, A.M. Gorman, A. Samali, Stress-induced self-cannibalism: on the regulation of autophagy by endoplasmic reticulum stress, Cell. Mol. Life Sci. 70 (2013) 2425–2441.
[46] W. B'Chir, A.C. Maurin, V. Carraro, J. Averous, C. Jousse, Y. Muranishi, et al., The eIF2alpha/ATF4 pathway is essential for stress-induced autophagy gene expression, Nucleic Acids Res. 41 (2013) 7683–7699.
[47] D. Senft, Z.A. Ronai, UPR, autophagy, and mitochondria crosstalk underlies the ER stress response, Trends Biochem. Sci. 40 (2015) 141–148.
[48] K. Moustaka, S. Katsiougiannis, R. Tenta, S. Havaki, P. Koutsoudaki, H.M. Moutsopoulos, et al., thu0223|chronic adrenergic stimulation of minor salivary glands of patients with primary sjögren's drives ER stress and activation OF the unfolded protein response, Ann. Rheum. Dis. 78 (2019) 389–390.
[49] M.J. Barrera, S. Aguilera, I. Castro, J. Cortes, V. Bahamondes, A.F.G. Quest, et al., Pro-inflammatory cytokines enhance ERAD and ATF6alpha pathway activity in salivary glands of Sjogren's syndrome patients, J. Autoimmun. 75 (2016) 68–81.
[50] E. Apostolou, P. Moustardas, T. Iwawaki, A.G. Tzioufas, G. Spyrou, Ablation of the chaperone protein ERdj5 results in a sjogren's syndrome-like phenotype in mice, consistent with an upregulated unfolded protein response in human patients, Front. Immunol. 10 (2019) 506.
[51] J. Petrasek, A. Iracheta-Vellve, T. Csak, A. Satishchandran, K. Kodys, E.A. Kurt-Jones, et al., STING-IRF3 pathway links endoplasmic reticulum stress with hepatocyte apoptosis in early alcoholic liver disease, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 16544–16549.
[52] L. Zeng, Y.P. Liu, H. Sha, H. Chen, L. Qi, J.A. Smith, XBP-1 couples endoplasmic reticulum stress to augmented IFN-beta induction via a cis-acting enhancer in macrophages, J. Immunol. 185 (2010) 2324–2330.
[53] P. Fang, L. Xiang, S. Huang, L. Jin, G. Zhou, L. Zhuge, et al., IRE1alpha-XBP1 signaling pathway regulates IL-6 expression and promotes progression of hepatocellular carcinoma, Oncol. Lett. 16 (2018) 4729–4736.
[54] A. Nezos, F. Gravani, A. Tassidou, E.K. Kapsogeorgou, M. Voulgarelis, M. Koutsilieris, et al., Type I and II interferon signatures in Sjogren's syndrome pathogenesis: contributions in distinct clinical phenotypes and Sjogren's related lymphomagenesis, J. Autoimmun. 63 (2015) 47–58.
[55] M. Xue, F. Fu, Y. Ma, X. Zhang, L. Li, L. Feng, et al., The PERK arm of the unfolded protein response negatively regulates transmissible gastroenteritis virus replication by suppressing protein translation and promoting type I interferon production, J. Virol. 92 (2018).
[56] Y.P. Liu, L. Zeng, A. Tian, A. Bomkamp, D. Rivera, D. Gutman, et al., Endoplasmic reticulum stress regulates the innate immunity critical transcription factor IRF3, J. Immunol. 189 (2012) 4630–4639.
[57] D. Prantner, D.J. Perkins, S.N. Vogel, AMP-activated kinase (AMPK) promotes innate immunity and antiviral defense through modulation of stimulator of interferon genes (STING) signaling, J. Biol. Chem. 292 (2017) 292–304.
[58] I. Dikic, Z. Elazar, Mechanism and medical implications of mammalian autophagy, Nat. Rev. Mol. Cell Biol. 19 (2018) 349–364.
[59] T. Riffelmacher, A. Clarke, F.C. Richter, A. Stranks, S. Pandey, S. Danielli, et al., Autophagy-dependent generation of free fatty acids is critical for normal neutrophil differentiation, Immunity 47 (2017) 466–480 e5.
[60] K. Palikaras, E. Lionaki, N. Tavernarakis, Mechanisms of mitophagy in cellular homeostasis, physiology and pathology, Nat. Cell Biol. 20 (2018) 1013–1022.
[61] J. Martinez, K. Verbist, R. Wang, D.R. Green, The relationship between metabolism and the autophagy machinery during the innate immune response, Cell Metabol. 17 (2013) 895–900.
[62] D. Carling, AMPK signalling in health and disease, Curr. Opin. Cell Biol. 45 (2017) 31–37.
[63] J. Kim, Y.C. Kim, C. Fang, R.C. Russell, J.H. Kim, W. Fan, et al., Differential regulation of distinct Vps34 complexes by AMPK in nutrient stress and autophagy, Cell 152 (2013) 290–303.
[64] I.K. Poon, C.D. Lucas, A.G. Rossi, K.S. Ravichandran, Apoptotic cell clearance: basic biology and therapeutic potential, Nat. Rev. Immunol. 14 (2014) 166–180.
[65] N. Yatim, H. Jusforgues-Saklani, S. Orozco, O. Schulz, R. Barreira da Silva, C. Reis e Sousa, et al., RIPK1 and NF-kappaB signaling in dying cells determines cross-priming of CD8(+) T cells, Science 350 (2015) 328–334.
[66] M. Obeid, A. Tesniere, F. Ghiringhelli, G.M. Fimia, L. Apetoh, J.L. Perfettini, et al., Calreticulin exposure dictates the immunogenicity of cancer cell death, Nat. Med. 13 (2007) 54–61.
[67] L. Galluzzi, F. Pietrocola, J.M. Bravo-San Pedro, R.K. Amaravadi, E.H. Baehrecke, F. Cecconi, et al., Autophagy in malignant transformation and cancer progression, EMBO J. 34 (2015) 856–880.
[68] A. Okuma, K. Hoshino, T. Ohba, S. Fukushi, S. Aiba, S. Akira, et al., Enhanced apoptosis by disruption of the STAT3-IkappaB-zeta signaling pathway in epithelial cells induces Sjogren's syndrome-like autoimmune disease, Immunity 38 (2013) 450–460.
[69] S. Esmaili, A. Xu, J. George, The multifaceted and controversial immunometabolic actions of adiponectin, Trends Endocrinol. Metab. 25 (2014) 444–451.
[70] C. Ding, L. Li, Y.C. Su, R.L. Xiang, X. Cong, H.K. Yu, et al., Adiponectin increases secretion of rat submandibular gland via adiponectin receptors-mediated AMPK signaling, PLoS One 8 (2013) e63878.
[71] Y.C. Su, R.L. Xiang, Y. Zhang, C. Ding, X. Cong, X.H. Guo, et al., Decreased submandibular adiponectin is involved in the progression of autoimmune sialoadenitis in non-obese diabetic mice, Oral Dis. 20 (2014) 744–755.
[72] M. Liu, F. Liu, Up- and down-regulation of adiponectin expression and multimerization: mechanisms and therapeutic implication, Biochimie 94 (2012) 2126–2130.
[73] A. Sahebkar, G.F. Watts, Fibrate therapy and circulating adiponectin concentrations: a systematic review and meta-analysis of randomized placebo-controlled trials, Atherosclerosis 230 (2013) 110–120.
[74] V. Dubois, J. Eeckhoute, P. Lefebvre, B. Staels, Distinct but complementary contributions of PPAR isotypes to energy homeostasis, J. Clin. Investig. 127 (2017) 1202–1214.
[75] A.G. Vakrakou, A. Polyzos, E.K. Kapsogeorgou, D. Thanos, M.N. Manoussakis, Impaired anti-inflammatory activity of PPARgamma in the salivary epithelia of Sjogren's syndrome patients imposed by intrinsic NF-kappaB activation, J. Autoimmun. 86 (2018) 62–74.
[76] X. Li, B. Xu, Y. Wang, L. Wei, Anti-inflammatory effect of peroxisome proliferator-activated receptor-gamma (PPAR-gamma) on non-obese diabetic mice with Sjogren's syndrome, Int. J. Clin. Exp. Pathol. 7 (2014) 4886–4894.
[77] T. Roy, I. Banerjee, S. Ghosh, R.S. Dhali, A. De Pati, S.K. Tripathi, Effects of co-treatment with pioglitazone and methotrexate on experimentally induced rheumatoid arthritis in Wistar albino rats, Indian J. Pharmacol. 49 (2017) 168–175.
[78] X. Shi-wen, M. Eastwood, R.J. Stratton, C.P. Denton, A. Leask, D.J. Abraham, Rosiglitazone alleviates the persistent fibrotic phenotype of lesional skin scleroderma fibroblasts, Rheumatology 49 (2010) 259–263.
[79] L. Dubuquoy, C. Rousseaux, X. Thuru, L. Peyrin-Biroulet, O. Romano, P. Chavatte, et al., PPARgamma as a new therapeutic target in inflammatory bowel diseases, Gut 55 (2006) 1341–1349.
[80] C.G. Su, X. Wen, S.T. Bailey, W. Jiang, S.M. Rangwala, S.A. Keilbaugh, et al., A novel therapy for colitis utilizing PPAR-gamma ligands to inhibit the epithelial inflammatory response, J. Clin. Investig. 104 (1999) 383–389.
[81] A.G. Tzioufas, A.V. Goules, Limited efficacy of targeted treatments in Sjogren's syndrome: why? Clin. Exp. Rheumatol. 36 (Suppl 112) (2018) 27–28.
[82] A.V. Maganti, S.A. Tersey, F. Syed, J.B. Nelson, S.C. Colvin, B. Maier, et al., Peroxisome proliferator-activated receptor-gamma activation augments the beta-cell unfolded protein response and rescues early glycemic deterioration and beta cell death in non-obese diabetic mice, J. Biol. Chem. 291 (2016) 22524–22533.