Accepted Manuscript

Title: T cells and their immunometabolism: a novel way to understanding sepsis immunopathogenesis and future therapeutics

Author: V. Kumar

PII: S0171-9335(18)30012-8
DOI: https://doi.org/10.1016/j.ejcb.2018.05.001
Reference: EJCB 51012

To appear in:

Received date: 8-1-2018
Revised date: 3-3-2018
Accepted date: 3-5-2018

Please cite this article as: Kumar V, T cells and their immunometabolism: a novel way to understanding sepsis immunopathogenesis and future therapeutics, *European Journal of Cell Biology* (2010), https://doi.org/10.1016/j.ejcb.2018.05.001

T cells and their immunometabolism: a novel way to understanding sepsis immunopathogenesis and future therapeutics

Kumar V[1,2]

[1]Children's Health Queensland Clinical Unit, School of Clinical Medicine, Mater Research, Faculty of Medicine, University of Queensland, ST Lucia, Brisbane, Queensland 4078, Australia

[2]School of Biomedical Sciences, Faculty of Medicine, University of Queensland, ST Lucia, Brisbane, Queensland 4078, Australia

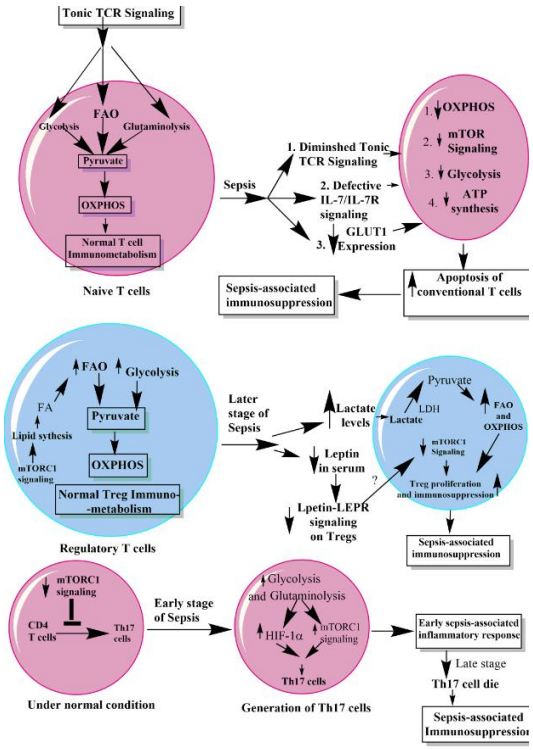
Running Title: T cell immunometabolism and sepsis

[*]Corresponding author

Dr Vijay Kumar (BSc. MSc. Ph.D.)

Research Fellow (Lecturer)
Department of Paediatrics and Child Care,
School of Medicine, Mater Research,
University of Queensland, ST Lucia, Brisbane, Queensland 4078, Australia
Email: vij_tox@yahoo.com, v.kumar3@uq.edu.au

Graphical Abstract



Highlights

- Despite advance in understanding the immunopathogenesis of sepsis we still do not have any direct therapeutic target to manage sepsis
- Beside affecting physiological metabolism, sepsis also affects metabolism of immune cells, here it is called immunometabolism
- T cells are an important component of adaptive immunity and are severely affected by sepsis as early as within three hours of onset of sepsis
- Regulatory T cells (Tregs) are responsible for the generation of a stage of immunosuppression in the later stage of sepsis
- Studying and targeting T cell and Treg immunometabolism at different stages of sepsis will provide novel therapeutic approaches against it

Abstract

Sepsis has always been considered as a big challenge for pharmaceutical companies in terms of discovering and designing new therapeutics. The pathogenesis of sepsis involves aberrant activation of innate immune cells (i.e. macrophages, neutrophils etc.) at early stages. However, a stage of immunosuppression is also observed during sepsis even in the patients who have recovered from it. This stage of immunosuppression is observed due to the loss of conventional (i.e. $CD4^+$, $CD8^+$) T cells, Th17 cells and an upregulation of regulatory T cells (Tregs). This process also impacts metabolic processes controlling immune cell metabolism called immunometabolism. The present review is focused on the T cell-mediated immune response, their immunometabolism and targeting T cell immunometabolism during sepsis as future therapeutic approach. The first part of the manuscripts describes an impact of sepsis on conventional T cells, Th17 cells and Tregs along with their impact on sepsis. The subsequent section further describes the immunometabolism of these cells ($CD4^+$, $CD8^+$, Th17, and Tregs) under normal conditions and during sepsis-induced immunosuppression. The article ends with the therapeutic targeting of T cell immunometabolism (both conventional T cells and Tregs) during sepsis as a future immunomodulatory approach for its management.

Key Words: Sepsis; Immunosuppression; Immunometabolism; T cells; Tregs

1. Introduction

Sepsis is known since at least 1,000 BC- under one or another condition, for example Ibna Sina (also known as Avicenna), an Islamic philosopher described sepsis as putrefaction of blood and tissues with fever (Majno, 1991). Thereafter, the term sepsis was used by Greek Physician called Hippocrates in 430 BC to describe the decomposition of organic matter or human body (Geroulanos and Douka, 2006; Jensen and Bouadma, 2016). The word sepsis is originally derived from a Greek word [σηψις] pronounced as *sipsis* = make rotten that was further derived from sepo [σηπω] that means "I rot" (Botero and Pérez, 2012; Funk et al., 2009; Geroulanos and Douka, 2006). Thus, sepsis was known to ancient physicians thousands of years before. However, its pathogenesis and cause was not clear to them. After the discoveries made by pioneer researchers including Ignaz Semmelweis (an early pioneer of antiseptic techniques), Louis Pasteur (inventor of a techniques called pasteurization and vaccination) and Joseph Lister (inventor of antiseptic surgery) a modern view of sepsis evolved (Marshall, 2004). However, the most modern definition of sepsis that is defined as an invasion of microorganisms and/or their toxins into the bloodstream, along with the organism's reaction against this invasion was given by US-American intensive care unit (ICU) specialist Roger C. Bone (1941-1997) that remained unchanged for more than two decades. However, currently according to sepsis-3 guidelines "sepsis is defined as a life-threatening organ dysfunction caused by dysregulated immune response during infection" (Singer et al., 2016).

Currently, we are in the most advanced stage of 21st Century medicine and it is further getting advanced every year but when it comes to sepsis, we are still lacking target based therapy to counter sepsis effectively. For example, an annual incidence of sepsis is 31.5 million that causes the death of 5.3 million peoples in the high-income countries throughout the world (Fleischmann et al., 2016). In addition to its high mortality, it also costs more than $14 billion dollars annually for managing sepsis patients admitted to ICUs in the United States alone (Healthcare and Utilization, 2008). Despite the advancements in the field of drug discovery and medicine, the increasing incidence of sepsis has made it a major public health problem (Finfer and Machado, 2016; Fleischmann et al., 2016; Healthcare and Utilization, 2008). For example, Drotrecogin alfa (activated), a recombinant activated protein C developed by Eli Lilly and Company, and marketed as Xigris, was the only FDA (USA) approved drug for the effective management of sepsis patients at advanced stage of the disease that has also been taken off the market in 2011 (Hosac, 2002; Ranieri et al., 2012). Thus, sepsis management is

still a critical medical condition to physicians working in intensive care units (ICUs). With the advancement in sepsis research we gained scientific knowledge regarding immunopathogenesis of sepsis and associated inflammatory immune response as reviewed extensively in references mentioned (Bosmann and Ward, 2013; Delano and Ward, 2016a, b; Hotchkiss et al., 2016; Hotchkiss et al., 2013; Kumar and Sharma, 2008; Lai et al., 2014; Venet and Monneret, 2017; Weber and Swirski, 2014).

Sepsis is a disease of hyperactivated immune response against the pathogen (Hotchkiss et al., 2016). But, a stage of immunosuppression also occurs simultaneously during the phase of hyperactivated innate immunity (Hotchkiss et al., 2016). This is because a loss of both B cells and T cells via apoptosis is observed during early phase of sepsis (Hotchkiss et al., 2001; Monserrat et al., 2013; Unsinger et al., 2006). This immunosuppression is characterized by lymphopenia and loss of immune function (Boomer et al., 2011; Weber and Swirski, 2014). The patients who survive the episode of sepsis often develop long-lasting stage of immunosuppression making them susceptible to develop certain secondary nosocomial infections along with various viral infections (Hotchkiss et al., 2009; Otto et al., 2011; Ward, 2012). An altered stage of metabolism is observed in immune cells (i.e. macrophages, and T cells etc.) during their activation that governs their further action (Ganeshan and Chawla, 2014; MacIver et al., 2013; Van den Bossche et al., 2017). A broad spectrum defect in metabolic stages of leukocytes during sepsis is mainly responsible for immunosuppression observed during a later stage of sepsis (Cheng et al., 2016). Thus, it becomes essential to study the immunometabolism of lymphocytes for targeting sepsis.

One of the major immune cell population that shows a profound decline during sepsis-associated immunosuppression/immunoparalysis comprises of T cells. The population of T cells decreases in various compartments of the body including lymph nodes, spleen, gut, lungs and in other vital organs (Boomer et al., 2011). Thus, present review is aimed to describe the role of T cells in the pathogenesis of sepsis, changes in their immunometabolic stage and targeting T cell immunometabolism in sepsis.

2. T cell-mediated immune response and the pathogenesis of sepsis

T cells are cellular component of adaptive immunity that provide support to proper functioning of other arms of immune system thus, acting as coordinators (for example, helper T (Th) cells provide support to all major components of innate and adaptive immunity via secreting various immunoregulatory molecules including cytokines and chemokines) and effector cells of adaptive immunity (i.e. cytotoxic T cells directly attack on tumours and virus-infected cells (Juno et al., 2017; Martinez-Lostao et al., 2015; Phetsouphanh et al., 2017; Rabb, 2002; Shinkai

et al., 2002). Additionally, T cells also regulate antibody production and associated antibody-mediated immune response (Figueiredo et al., 2017; Sage et al., 2016). Thus, T cells are a very important component of the mammalian immune system and their deficiency, dysregulation/abnormal function is associated with various immunodeficiency and autoimmune diseases (Bluestone et al., 2015; Dornmair et al., 2003; Liston et al., 2008).

2.1. $CD4^+$, $CD8^+$ and $CD4^+CD8^+$ T cells in sepsis

The direct role of T cells in the immunopathogenesis of sepsis seems to be very complex. For example, gram-negative bacterial peritonitis (i.e. *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*) causing sepsis in mice induces a profound decrease in thymocytes as soon as 3-hours post sepsis and within 3 days maximum damage to thymus and T cells is reported (Wang et al., 1994). The most prominently decreased population of T cells comprises of $CD4^+CD8^+$ T cells (Wang et al., 1994). An early induction of T cell apoptosis in mouse model of sepsis indicates that these cells are crucial to providing protection against sepsis (Hotchkiss et al., 1999a). This is because mice deficient in T cells die early due to sepsis (Hotchkiss et al., 1999b). The overexpression of anti-apoptotic *Bcl-2* gene specifically in T cells prevented apoptotic loss of T cells upon induction of sepsis and increased the survival (Hotchkiss et al., 1999b). This is further strengthened by the observation that adoptive transfer of T cells to T-cell deficient mice provides protection against sepsis (Shelley et al., 2003). $CD4^+$ T cells provide protection to host against sepsis as CD4 KO succumb to sepsis earlier than their wild-type (WT) counterparts (Martignoni et al., 2008). Sepsis-induced loss of mitochondrial membrane potential in T cells has also been observed (Hotchkiss et al., 1999b).

The loss of immunocompetent $CD4^+CD8^+$ T cells is also reported in patient with severe sepsis (Boomer et al., 2011; Inoue et al., 2013). A highly exhausted immunophenotype of T cells is observed in the spleen of patients surviving sepsis (Boomer et al., 2011; Inoue et al., 2013). The loss of $CD4^+$ T cells in humans during sepsis occurs due to the profound activation of caspase 3 and 9 (indicators of apoptotic cells death) (Hotchkiss et al., 1999a; Hotchkiss et al., 2001). Sepsis-associated apoptosis of both $CD4^+$ and $CD8^+$ T cells is responsible for the development of lymphopenia and immunosuppression in patients at later stages of sepsis (Cabrera-Perez et al., 2014; Condotta et al., 2013; Rimmele et al., 2016). Sepsis also impairs their functional ability to proliferate in response to antigen-mediated stimulation and their effector functions (Danahy et al., 2016). Thus, sepsis-induced defect in $CD4^+$ and $CD8^+$ T cells both quantitatively and qualitatively increases susceptibility to developing secondary infections in sepsis patients along with its survivors (Danahy et al., 2016). Further research in this direction has shown that the full activation of $CD4^+$ T cells during sepsis requires their

stimulation with specific antigen (Schmoeckel et al., 2015). Thus, an incomplete/partial stimulation of $CD4^+$ T and $CD8^+$ T cells during sepsis in a T-cell receptor (TCR)-independent manner may cause their increased apoptosis (Esser et al., 2001). Whereas their full stimulation and proliferation in the presence of a specific antigen can alter apoptotic cell death, lymphopenia and a stage immunosuppression during sepsis. This needs to be studied effectively and may prove helpful to design T cell-based immunomodulatory therapeutics to target sepsis.

Furthermore, the onset of sepsis and septic shock in humans is associated with decreased expression of T-bet, GATA3, and ROR-γt—transcription factors that regulate the Th1, Th2, and Th17 effector $CD4^+$ T cell phenotypes (Pachot et al., 2005). $CD4^+CD62L^+$ T cells isolated from mice with sepsis showed reduced proliferative capacity, altered gene expression and repressive histone methylation (i.e. (i.e. increased methylation of H3K27) (Carson et al., 2010). Thus, sepsis has a potential to affect both genes controlling epigenetic switch via chromatin remodeling and an induction of transcription factor that can potentially modify the phenotype and function of $CD4^+$ T cells observed during sepsis (Carson et al., 2010; Jensen et al., 2018).

2.2. Th17 cells in sepsis

Th17 cells are different type of $CD4^+$T cells that express lineage-specific transcription factor, RORγt and secrete IL-17A and IL-17F cytokines (Brucklacher-Waldert et al., 2009; Maddur et al., 2012). Human Th17 cells also express T-bet transcription factor along with retinoic-acid-receptor-related orphan nuclear receptor gamma t (RORγt) and can produce IFN-γ in the presence of IL-12 (Romagnani et al., 2009). Th17 cells can be differentiated form naïve $CD4^+$ T cells in mice in the presence of transforming growth factor (TGF)-β and the cytokine, IL-6 in mice (Binger et al., 2017). The involvement of transforming growth factor (TGF)-β in the differentiation of Th17 cells depicts a close relationship between the cells of Th17 lineage and CD4+CD25+Foxp3+ regulatory T cells (Tregs) (Korn et al., 2009). Th17 cells are primarily associated with several autoimmune diseases including psoriasis, rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and multiple sclerosis (MS) (Yang et al., 2014). However, Th17 cells also provide defence against extracellular pathogens including fungi (i.e. *candida albicans*) and bacteria (i.e. *Klebsiella pneumoniae, Bordetella pertussis,* or *Streptococcus pneumoniae* etc.) colonizing mucosal surfaces (Maddur et al., 2012; Peck and Mellins, 2010). Thus their deficiency can prove detrimental to the host during defence against infectious diseases. For example diminished Th17 immune response during severe sepsis is associated with an increased mortality (Wu et al., 2013). However, blood samples taken on admission (Day 0) showed higher number of Th17 cells but their number decreased by day 7 (Brunialti et

al., 2012). Thus, this decrease in Th17 cells proves detrimental to septic patients via promoting immunoparalysis/immunosuppression (Rendon and Choudhry, 2012). An association between imbalanced Th17 and regulatory T cells (Tregs) cell population during multi-organ dysfunction syndrome (MODS) including acute respiratory distress syndrome (ARDS) is also observed during sepsis (Guo et al., 2017; Yu et al., 2015a). The decreased Th17 immune response during sepsis increases the chance to developing fungal infections including *Candida albicans* (van de Veerdonk et al., 2012). The exact role of Th17 cells during sepsis remains to be established.

2.3. Regulatory T (Tregs) cells in sepsis

Tregs like other T cells also develop and get matured in thymus and survive in the periphery including peripheral blood circulation and various target organs (Belkaid and Rouse, 2005).. Tregs continuously express a unique transcription factor called FOXP3 (Forkhead box P3) or scurfin that is required for their generation (Fontenot and Rudensky, 2005). Tregs are $CD25^{+}CD4^{+}FOXP3^{+}$ T cells continuously expressing CTLA-4 (cytotoxic-T-lymphocyte-associated protein-4) or CD152 and glucocorticoid-inducible tumor necrosis factor receptor (GITR) (Belkaid and Rouse, 2005; Fontenot and Rudensky, 2005; Piccirillo and Shevach, 2004). The importance of Tregs in humans can be exemplified by the occurrence of IPEX (Immunodysregulation polyendocrinopathy enteropathy X-linked) syndrome that occurs due to the *FOXP3* gene (located on chromosome Xp11.23) mutation and in scurfy strain mice (Bacchetta et al., 2006; Bennett et al., 2001; Newton et al., 2016; Smyk-Pearson et al., 2003). However, in addition to these natural Tregs that can be further classified into thymus-derived Tregs (tTregs) and peripherally induced Tregs (pTregs), a distinct population of Tregs can be induced by various microbial antigens and foreign antigens in the periphery and are called induced Tregs or *in vitro* generated Tregs (iTregs) (Mills and McGuirk, 2004). tTregs are most natural form of Tregs as they express FoxP3 constitutively, while pTRegs are generated upon encounter with antigens in peripheral tissue or circulation environment (Newton et al., 2016). Due to these differences all these Tregs (i.e. tTregs, pTregs and iTregs) may not exhibit a similar immunometabolism at their naïve or activated stage (Newton et al., 2016). Tregs are major immunoregulatory cells with a potential to suppress exaggerated pro-inflammatory action of effector T cells or Teffs that are type of activated T cells (i.e. activated Th1, Th2, Th3, Th9, Th17, cytotoxic T cells etc.) getting activated via different mechanisms described elsewhere (Arce-Sillas et al., 2016; Pandiyan et al., 2011; Schmidt et al., 2012).

An association of Tregs with sepsis-associated immunoparalysis is also reported (Monneret et al., 2003). These patients showed 56% mortality at 28 days post-admission into ICU (Monneret et al., 2003). Thus, an increase in immunosuppressive Tregs in patients with

sepsis is associated with immunoparalysis. This immunosuppression or immunoparalysis can act as one of the contributing factor for sepsis-associated mortality. The number of Tregs in peripheral circulation of septic patients increases within three days of the development of septic shock (Hein et al., 2010). A profound increase in $CD4^+CD25^+FOXP3^+$ regulatory T cells in the spleen during sepsis is also observed (Hein et al., 2010; Scumpia et al., 2006). The use of DEREG (DEpletion of REGulatory T cells) mice further showed an increase in $Foxp3^+$ Treg cells during murine sepsis (Tatura et al., 2015). In addition, both the populations of nTregs [i.e. natural Tregs ($Nrp1^+$ $Foxp3^+$) and iTregs ($Nrp1^-$ $Foxp3^+$)] are stable with unmethylated form of *foxp3-TSDR* and act as immunosuppressive T cells during sepsis (Tatura et al., 2015). DEREG mice showed phenotype of severe sepsis with higher circulating IL-6 levels and higher mortality rate in comparison to non-depleted DEREG mice during early phase of sepsis (Tatura et al., 2015). Thus, $Foxp3^+$ Treg cells limit the hyper-inflammatory response and accelerate recovery during early phase of sepsis (Tatura et al., 2015).

An increase in $CD4^+CD25^+CD127^-$ cells among sepsis patients (3–7 days after onset of the septic shock) is found to be correlated with a decrease in the number of $CD4^+$ T cells due to the selective depletion of $CD4^+CD25^-$ T cells (Monneret et al., 2003; Venet et al., 2009; Venet et al., 2004). Additionally, an increased number of Tregs in septic patients can also be observed due to an increase in transcription-permissive histone modification of the *Foxp3* that might skew T cell differentiation towards Treg cell lineage development during sepsis (Cavassani et al., 2010). IL-33 is also reported to increase the number of Tregs during sepsis and long-term immunosuppression (Nascimento et al., 2017). This is because a higher levels of Tregs, IL-33, and IL-10 are observed in peripheral circulation of patients surviving sepsis (Nascimento et al., 2017). In humans Treg mediated immunosuppression proves detrimental to septic patients (Cao et al., 2015; Kessel et al., 2009). Tregs with a previous experience of a pro-inflammatory environment reversed several activation-induced changes and lost their enhanced immunosuppressive function with time (van der Veeken et al., 2016). This phenotype of Tregs in sepsis needs to be studied carefully as this can provide a direction in designing future therapeutic approaches.

3. Immunometabolism among different T cell subsets and sepsis

Immunometabolism is relatively a new branch of immunology although metabolic changes in neutrophils and macrophages were observed more than 50 years back in 1964 during the process of phagocytosis (Rossi et al., 1972; Rossi and Zatti, 1964). Furthermore, the metabolic shift form oxidative phosphorylation (OXPHOS) to glycolysis was described in peritoneal macrophages and neutrophils subjected to phagocytosis as early as in 1963 (Oren et al., 1963).

Thus, the shift from OXPHOS to glycolysis during conditions of high energy demand including cancers, severe infections or sepsis called is called Warburg effect (Ferreira, 2010; Hsu and Sabatini, 2008). The Warburg effect was first described in cancer cells that utilize glucose via glycolysis as a major source of energy for their survival and growth (Ferreira, 2010; Hsu and Sabatini, 2008; Koppenol et al., 2011). Pro-inflammatory T cell populations that include Th1, Th2, and Th17 cells exhibit increased glycolysis but less OXPHOS than *in vitro*-induced iTregs that utilize lipid peroxidation (LPO) or fatty acid oxidation (FAO) and OXPHOS mainly for their energy requirement (Michalek et al., 2011; Shi et al., 2011).

The activation, growth, division, proliferation and the involvement of immune cells into their effector function and then returning back to their homeostatic condition is tightly regulated by their metabolic status (Buck et al., 2017). The shift towards a particular pathway controlling the immunometabolism of T cells is determined by several factors including nutrient availability, energy status and requirement along with the cell's own internal metabolic status including hypoxia or internal generation of reactive oxygen species (ROS) and balance between internal metabolites (Buck et al., 2017). Naïve T cells ((Tn) maintain a balance between oxidizing by-products including ROS and reducing agents including cellular antioxidants (i.e. glutathione (GSH), superoxide dismutase (SOD) etc.) (Franchina et al., 2018; Kamiński et al., 2012; Mak et al., 2017; Terrazzano et al., 2014). Thus, it is the level of intracellular ROS that guides and diversifies the outcome of ROS-associated intracellular signalling events responsible for T cell immunometabolism and its reprogramming (Franchina et al., 2018) Tn keep check in production of excessive ROS via constant production of antioxidant molecules to prevent ROS-mediated cell death (Gorrini et al., 2013; Panieri and Santoro, 2016). ROS generated in T cell mitochondria (mROS) is shown to play an important role in the activation of mTOR and Myc pathways involved in T cell immunometabolism (Franchina et al., 2018). For example, blockade of ROS inhibited $CD4^{+}$T cell immune response via inhibiting mTOR signalling and reduced transition to aerobic glycolysis due to deceased Myc and glucose transporter 1 (GLUT1) upregulation, decreased glucose uptake and decreased production of lactate (Previte et al., 2017; Previte and Piganelli, 2017)

The factors controlling immunometabolism among different T cell subsets can also impact immune phenotype for example, hypoxia-inducible factor (HIF)-1α regulates the balance among Tregs and Th17 cells (Dang et al., 2011). This is because HIF-1α directly increases the development of Th17 cells via activating and forming a complex with RORγt and recruiting p300 to the IL-17 promoter region that further regulates activation of Th17 signature genes (Dang et al., 2011). While, it inhibits the development of Tregs by binding to Foxp3 and

degrading it by ubiquitin-proteasome system under both normoxia and hypoxic conditions (Dang et al., 2011). This is because mice deficient in HIF-1α are resistant to the induction of Th17 mediated inflammatory disease including experimental autoimmune encephalitis (EAE) due to diminished Th17 cells and increased levels of Tregs (Dang et al., 2011). Thus, immunometabolism determines the cellular fate of T cells and their immunological function under various pathological conditions including cancers, infections and autoimmune diseases (Clever et al., 2016; Doedens et al., 2013; Sun et al., 2017; Weyand and Goronzy, 2017; Weyand et al., 2017; Yang et al., 2015). Following sections are designed to describe the immunometabolic changes among different populations of T cells and their targeting to manage sepsis and sepsis-associated immunosuppression.

3.1. Immunometabolic shift in $CD4^+$, $CD8^+$ and $CD4^+CD8^+$T cells during sepsis

The immunometabolic stages and requirements of all the stages and types of T cells is discussed somewhere else in detail (Coe et al., 2014; Johnson et al., 2016; MacIver et al., 2013). The quiescent or naïve T cells are dependent on oxidative phosphorylation (OXPHOS) for their energy demand (Chapman et al., 2017). The pyruvic acid/pyruvate required for OXPHOS is obtained from glucose (i.e. glycolysis), fatty acid oxidation (FAO) or amino acid metabolism (i.e. glutaminolysis) (Chapman et al., 2017; MacIver et al., 2013) (Fig.1). This glucose requirement is controlled by its uptake regulated by tonic TCR signaling that is defined as a low-level TCR signaling in response to self-peptide/MHC molecules and IL-7/IL-7receptor signaling required for the survival of naïve T cells (Chapman et al., 2017). Therefore absence of tonic TCR signaling may cause decreased GLUT1 (also known as SLC2A1) expression and decreased glucose uptake that may lead to the death of naïve T cells and their atrophy (Rathmell et al., 2000). For example, if T cells are removed from their normal microinches, they internalize and degrade GLUT1 along with other nutrient transporters to prevent required/sufficient nutrient uptake for the maintenance of their viability (MacIver et al., 2013). IL-7R signaling via STAT5 causes delayed but sustained activation of Akt-signaling that promotes glucose uptake through the upregulation of surface expression of GLUT1 and prevents apoptotic cell death (Wofford et al., 2008) (Fig. 1). Deletion of *Glut1* gene selectively limits $CD4^+$, but not $CD8^+$ T cell glycolytic reprogramming and their proliferation (Cao et al., 2014; Macintyre et al., 2014). This indicates an important role of other GLUT family members in controlling glucose uptake in $CD8^+$ T cells (Cao et al., 2014; Macintyre et al., 2014). For example, an elevation of GLUT3 and GLUT6 is observed in GLUT1-deficient murine $CD8^+$ T cells but their role in the regulation of $CD8^+$ T cell immunometabolism and differentiation remains to be confirmed (Macintyre et al., 2014; Zhang and Romero, 2018).

Glutamine is the most abundant amino acid (AA) in circulation and an increased uptake of glutamine via glutamine receptors occurs in activated T cells in a MYC-dependent manner (Bantug et al., 2018; Wang et al., 2011). c-Myc is one of the most upregulated transcription factors (TFs) that gets activated upon T cell activation and also controls an expression of CD98 or large neutral amino acid transporter 1 (LAT1) (Wang et al., 2011). This is because an impaired expression of CD98 is observed in *c-myc* KO murine T cells (Wang et al., 2011). Thus, in activated conventional T cells MYC-signalling is a major regulator of glutaminolysis and its association with polyamine biosynthetic pathway (Wang et al., 2011). The deletion of MYC in activated T cells is associated with reduced ornithine and putrescine abundance causing a decreased T cell proliferation (Bantug et al., 2018). However, c-Myc activation does not stays continuously for longer duration after the activation of T cells (Best et al., 2013; Nie et al., 2012). c-Myc activation stimulates another transcription factor called activating enhancer-binding protein 4 (AP-4) that maintains aerobic glycolysis initiated by c-Myc to further support T cells population expansion (Chou et al., 2014; Karmaus and Chi, 2014). Mice lacking specifically AP4 in CD8 T cells are more susceptible to viral infections caused by West Nile virus (Chou et al., 2014). Additionally, AP-4 transcription factor in B cells is also associated with resolution of viral infections by amplifying the germinal centre (GC) B cell responses including sustained proliferation of B cells in GC and subsequent production of a diverse and protective antibody repertoire (Chou et al., 2016). However, the role of AP-4 in T cells during sepsis remains to be studied.

An increased uptake of leucine by effector $CD8^+$ T cells during *Listeria monocytogenes* infection is observed due to an upregulation of SLC7A5, a L (leucine-preferring system) transporter essential for leucine or large neutral amino acids (LNAAs) (Sinclair et al., 2013). The loss of leucine transporter SLC7A5 causes a decrease in T cell activation and effector maturation that depends on mTORC1 activity (Sinclair et al., 2013). This is because mTOR activity is also regulated by leucine through leucine sensor sestrin 2 (SESN2) (Wolfson et al., 2016). SESN2 acts as a GATOR2-interacting protein that binds to GATOR2 and SESN2-GATOR2 complex inhibits mTORC1 signaling under leucine deficit conditions (Saxton et al., 2016; Wolfson et al., 2016). A decreased basal protein synthesis is observed during sepsis in skeletal muscles (Laufenberg et al., 2014). Even oral leucine supplementation after 1 hour of sepsis fails to increase protein synthesis (Laufenberg et al., 2014). Furthermore it does not increase the process of protein synthesis and full activation of mTOR signaling pathway (Laufenberg et al., 2014). This impairment of leucine uptake and mTORC1 signaling during sepsis is also observed by another group (Kazi et al., 2011). These studies give us the basis to

study the impact of leucine on T cells isolated from septic patients undergone a stage of immunosuppression due to the loss of activated T cells where leucine controls mTORC1 signaling required for their activation and effector function (Sinclair et al., 2013).

mTOR is an atypical serine/threonine kinase that belongs to the phosphoinositide 3-kinase (PI3-K)-related kinase family and forms two different complexes called mTORC1 and mTORC2 by interacting with several proteins (Laplante and Sabatini, 2012). Both mTORC1 and mTORC2 integrate various external and internal signals associated with nutrient concentration, energy requirement, and various stressful condition including infections to regulate cellular metabolic requirements as per their immunological status (Laplante and Sabatini, 2012). The mTORC1 has its six known protein components, while mTORC2 has seven components (Laplante and Sabatini, 2012). The proper balance between mTORC1 and mTORC2 signaling is also involved in immunometabolism of naïve T cells (Chapman et al., 2017; Chi, 2012; Yang and Chi, 2012). For example, lack of tuberous sclerosis complex 1 or TSC1 (a repressor of mTOR) causes an increased activity of mTORC1 signaling causing a metabolic dysfunction among naïve T cells and their apoptotic death (Chi, 2012; O'Brien et al., 2011; Wu et al., 2011). Furthermore, this TSC1 activation is controlled by AMPK (5'Adenosine monophosphate-activated protein kinase) under different stimulatory conditions including metabolic stressors (metformin) and nutrient limitations (Blagih et al., 2015; Pearce et al., 2009; Rolf et al., 2013). Thus, AMPK via TSC1 acts as a negative regulator of mTORC1 and inhibits lipid synthesis but enhances FAO (Fatty acid oxidation) through phosphorylation and inactivation of Acetyl-CoA carboxylase (ACC) 1 and 2 (Davies et al., 1990; Faubert et al., 2013; Ma et al., 2017; Pearce et al., 2009). AMPK also inhibits HIF-1α induced glycolysis (Faubert et al., 2013). Thus, under healthy conditions, T cells are dependent on OXPHOS for their energy demand. However, as mentioned previously an increase in the apoptosis of T cells is observed in both humans and animal models of sepsis at the very early stages of sepsis. Until now it was not cleared what population of T cells gets affected during sepsis but a recent study has shown that sepsis and systemic inflammation cause loss of naïve T cells via increased apoptosis (Markwart et al., 2014). And, prevention of T cells apoptosis proved beneficial to host suffering from sepsis as mentioned previously.

Sepsis patients exhibit lowest levels of IL-7 in their serum (Andreu-Ballester et al., 2014). Also, transcriptomic analysis of peripheral blood lymphocytes isolated from blood taken from sepsis patients showed significantly decreased expression of IL-7R on T lymphocytes (Bauer et al., 2016). Thus, a defective IL-7/IL-7R signaling is an invited event during sepsis. IL-7 signaling via IL-7R on naive T cells is required to maintain their healthy immunometabolic stage via

upregulating glucose uptake through upregulation of expression GLUT1 (Wofford et al., 2008). Hence, IL-7 signaling is required to maintain normal immunometabolic stage of T cells. Thus a profound decrease in serum levels of IL-7 in sepsis patient may inhibit this signaling causing their apoptotic cell death. For example, T cells isolated from septic patients exhibited a significant decrease in basal levels of ATP molecules along with a decrease in OXPHOS and glycolysis pathways (Venet et al., 2017). Even T cells isolated from septic patient upon stimulation failed to induce glycolysis, OXPHOS, ATP production, GLUT1 expression (Venet et al., 2017). These T cells also showed impaired glucose uptake required for their survival, growth, and proliferation in comparison to control T cells due to defective mTOR signaling and AMPKα1 phosphorylation (Venet et al., 2017). However, no alteration in HIF-1α and Akt signaling was observed (Venet et al., 2017).

Akt is involved in the regulation of nutrient transporter expression, phosphorylation of the glycolytic enzyme hexokinase II (HKII) that promotes its localization to the mitochondria and enhances its enzymatic activity required for aerobic glycolysis (John et al., 2011; Roberts and Miyamoto, 2015; Roberts et al., 2013). A treatment with IL-7 improves the mTOR activation, GLUT1 surface expression, and glucose uptake by T cells isolated from septic patients (Venet et al., 2017). As inhibition of mTOR signaling with rapamycin treatment inhibited the effect of recombinant IL-7 treatment it can be an inference that IL-7 mediated protective effect on T cells is centrally mediated by mTOR signaling. Both mTOR and Akt promote aerobic glycolysis among T cells to support their growth, differentiation, and function (Delgoffe et al., 2011; Pollizzi et al., 2015). Thus, alteration of mTOR signaling may be responsible for an increased apoptosis of T cells during sepsis. Even treatment with recombinant human IL-7 (rhIL-7) has shown an increase in survival of animals subjected to CLP-induced sepsis and fungal sepsis (Patil et al., 2016; Shindo et al., 2017). In addition, rhIL-7 mediated immunotherapy has also increased the survival of animals subjected to two-hit model of *Pseudomonas aeruginosa* pneumonia (sublethal CLP-sepsis + *Pseudomonas aeruginosa* pneumonia) (Shindo et al., 2017). rhIL-7 treatment increased the population of innate lymphoid cells (ILCs) and $CD8^+$ T cells in lungs that secrete IL-17, IFN-γ, and TNF-α along with IFN-γ- and TNF-α-producing T cells and ILCs in spleen (Shindo et al., 2017). Thus, IL-7 has a potential to target altered immunometabolic stage of T cells during sepsis. The next step in this direction has been taken and rhIL-7 based immunomodulatory action in sepsis is currently ended with phase 2 clinical trial in USA and France (Venet and Monneret, 2017; Venet et al., 2018). The results of this phase 2 clinical trials are expected to get published in 2018 (Venet and Monneret, 2017; Venet et al., 2018).

Glutathione (GSH) plays an important role in priming T cell function during inflammatory conditions like sepsis or severe sepsis (Mak et al., 2017). Murine T cells deficient in GSH initially showed normal activation response but could not stayed for longer due to defective supply of energy and biosynthetic requirements (Mak et al., 2017). GSH-deficient T cells showed defective mTORC1 signaling, activation of c-Myc and nuclear factor of activated T cell (NFAT) that further damped the immunometabolic reprogramming required for increased energy demand during infection or inflammatory conditions (Mak et al., 2017). A decreased level of GSH in circulation, liver, and muscles of patients with sepsis and septic shock is observed (Fläring and Wernerman, 2008; Flaring et al., 2005; Flaring et al., 2003; Keller et al., 1985). Furthermore, GSH treatment has shown protection during lethal sepsis via enhancing innate immune response (Villa et al., 2002). Thus the levels of GSH in T cells during sepsis remains to be established as an increased apoptosis of these T cells is observed during sepsis. And if GSH deficiency stays for longer period of time it can lead decreased energy in these T cells that will ultimately end up with their apoptotic cell death (Mak et al., 2017).

3.2. Th17 cell immunometabolism during homeostasis and sepsis

Interest in Th17 cell immunology, regulation and function particularly arose within immunologist's community due to their particular role in various autoimmune inflammatory conditions including psoriasis, IBD, MS and RA etc. and in cancer (Asadzadeh et al., 2017; Bailey et al., 2014; Guery and Hugues, 2015; Ye et al., 2013). However, the ratio of Th17 cells and Tregs impacts the outcome of inflammatory conditions associated with these immune cells including infections (Diller et al., 2016; Ma et al., 2015; Sehrawat and Rouse, 2017). For example, as described in previous section that Th17/Treg ratio during sepsis plays an important role in MODS observed during sepsis (Guo et al., 2017; Yu et al., 2015a). Immunometabolic pathways control the balance between Th17 and Tregs (Sun et al., 2017).

The immunometabolic pathway involved in the generation of Th17 cells is governed by PI3K-Akt-mTORC1-S6K1 axis that suppresses *Gfi1*, a zinc finger protein that acts as a transcriptional repressor protein (Kurebayashi et al., 2012). This induction of Th17 cell differentiation also involves S6K1 that binds to the RORγt and carries it to the nucleus and thus inducing the genes responsible for the functional phenotype of Th17 cells (Kurebayashi et al., 2012). Experimental studies in mice have indicated that lack of mTORC1 signaling in naive CD4+ T cells prevents the differentiation of these cells into the Th1 and Th17 cell lineages both *in vitro* and *in vivo* without affecting their ability to differentiate into Th2 cells (Delgoffe et al., 2011; Sasaki et al., 2016). Thus induction of HIF-1α, activation of mTORC1 signalling pathway via increased glycolysis, glutaminolysis in $CD4^{+}$T cells may provide an environment

for the generation of Th17 cells during sepsis as loss of $CD4^+$ T cells and an increase in Th17 cells during early stages of sepsis is observed in clinical setting (Brunialti et al., 2012; Hotchkiss et al., 1999a; Hotchkiss et al., 2001; Nakaya et al., 2014; Poffenberger and Jones, 2014). This needs to be further studied in animal model of the disease.

HIF-1α is demonstrated to be a critical regulator of Th17 cell development as compared to induced-Tregs (iTregs) (Wang and Solt, 2016). Both Human and mice Th17 cells highly express HIF-1α and need it along with mTORC1 to synthesize and release IL-17 (Dang et al., 2011; Kastirr et al., 2015; Palazon et al., 2014; Shi et al., 2011). Loss of HIF-1α in T cells impacts glycolysis via affecting several genes controlling enzymes and proteins [i.e. GLUT1, Hexokinase II (HKII), Pyruvate kinase muscle (PKM), and Lactate dehydrogenase (LDH)], involved in glycolysis (Shi et al., 2011). An increase in HIF-1α is observed in the sepsis and septic shock patients (Textoris et al., 2012). Furthermore, a recent clinical study has shown the upregulation of HIF-1α in the blood of sepsis patients within 24 hours of first diagnosis of the disease (ClinicalTrials.gov (NCT number: NCT02163473). Furthermore animal models of sepsis have also shown an increase in HIF-1α during early stages of sepsis and its deletion proved beneficial to the host (Peyssonnaux et al., 2007; Werth et al., 2010). This is a stage where $CD4^+$, $CD8^+$ T cells undergo apoptosis but Th17 cells are seen to be upregulated and mounting an inflammatory response. This needs to be studied extensively to target immunometabolism very specifically and precisely to regulate T cell based immune response during sepsis.

AMPK acts as a negative regulator of mTORC1 signaling, thus may inhibit the generation of Th17 cells and associated inflammatory immune response. This is shown in a study where $AMPK\alpha1^{-/-}$ T cells exhibited decreased Th17 response against bacterial and viral pathogens in animal models (Blagih et al., 2015). However, the exact role of AMPK in Th17 immunometabolism remains to be studied for understanding its role in during sepsis and other inflammatory conditions. Th17 cells specifically depend on acetyl-coA carboxylase 1 (ACC1) for fatty acid synthesis (FAS) required for their activation and growth (Lochner et al., 2015). Th17 cells are mainly dependent on *de novo* FAS and do not depend on exogenously supplied glucose-derived carbon source generated through glycolysis or TCA cycle for their growth, division, and proliferation (Berod et al., 2014). An inhibition of FASN activity via Soraphen A (an ACC-specific inhibitor) or $ACC\text{-}1^{-/-}$ T cells showed defective differentiation towards Th17 cells (Berod et al., 2014). Studies are needed in this direction to explore the reluctance of Th17 cells to utilize external carbon source for their FAS under *in vivo* conditions. Thus under inflammatory conditions Th17 cells require increased glucose uptake that is met by increased

aerobic glycolysis (Binger et al., 2017) but Tregs enhance their lipid or fatty acid uptake to utilized energy-efficient pathways including FAO and OXPHOS (Almeida et al., 2016; MacIver et al., 2013; Park and Pan, 2015; Wang and Solt, 2016)

3.3. Immunometabolic control of Tregs function during sepsis

Naturally occurring regulatory T cells (Tregs) have a unique metabolic signature that distinguishes them from conventional Teff cells under *in vitro* conditions (Coe et al., 2014). For example, Tregs do not rely on significant rates of glycolysis (due to low levels of surface expression of GLUT1) as used by effector T cell (Teffs) (Coe et al., 2014; Johnson et al., 2016; Michalek et al., 2011). Instead, these natural Tregs exhibit high lipid oxidation rates under *in vitro* conditions (Michalek et al., 2011) For example, Teffs use increased glucose and glutamine uptake (Johnson et al., 2016). Natural Tregs have higher number of mitochondria with greater function/activity as compared to conventional $CD4^{+}$T cells *ex vivo* (Beier et al., 2015). However, Tregs developing *in vivo* exhibit similar immunometabolic phenotype that is glycolysis driven lipid synthesis for their survival and proliferation as shown by Teffs (Newton et al., 2016; Zeng et al., 2013).

The inhibition of glycolysis and glutaminolysis with 2-deoxyglucose (2-DG) and 6-diazo-5-oxo-L-norleucine (DON) and an enhancement of FAO with metformin diminishes proliferation of Tregs *in vivo* along with Teffs (Lee et al., 2015a). While iTregs have increased mitochondrial function as compared to other helper T cells subsets (i.e. Th1, Th2, Th3, Th9, and Th17 etc.) *in vitro* (Michalek et al., 2011; Zeng et al., 2013). Furthermore, CPT1α (Carnitine palmitoyltransferase Iα) inhibitor called etomoxir potentially limits differentiation of murine iTregs without affecting the generation of Th17 cell (Michalek et al., 2011; Xu et al., 2003), while metformin-mediated activation of AMPK causes an increase in differentiation of iTregs both *in vitro* and *in vivo* (Michalek et al., 2011). Tregs with higher CD25 expression exhibit an increased expression of FOXP3 in the presence of etomoxir (Chapman et al., 2017). Thus these Tregs exhibit higher immunosuppressive activity than iTregs generated in the absence of the drug (Chapman et al., 2017) The homeostatic functions of Tregs are independent of AMPKα1 (Rao et al., 2015). Hence, the elevated levels of FAO and AMPK activity in Tregs and iTregs under *ex vivo* conditions are only partially responsible for mitochondrial action required for Treg function (Michalek et al., 2011).

Kynurenine a metabolic product of tryptophan metabolism is shown to promote the generation of iTregs via binding to aryl-hydrocarbon receptor (Ahr) (Buck et al., 2015; Mezrich et al., 2010). A higher circulating level of kynurenine is observed in sepsis patients due to the overactivation of indoleamine 2,3-dioxygenase (IDO) that exerts several effects including

sepsis associated cognitive impairment and hypotension (Changsirivathanathamrong et al., 2011; Gao et al., 2016). Mice subjected to sepsis-associated encephalopathy (SAE) induced cognitive impairment showed protection upon treatment with an IDO inhibitor called 1-methyl-D, L-tryptophan (Gao et al., 2016). Another study has shown an association between higher plasma kynurenine levels and immunosuppression due to loss of $CD4^+$ and $CD8^+$ T cells during sepsis (Darcy et al., 2011). An association between increased Tregs, elevated IDO activity, and imbalanced kynurenine pathway is observed in interferon-positive primary Sjögren's syndrome (PSS) (Maria et al., 2016). Thus it will be interesting to observe the impact of kynurenine levels on Tregs in sepsis and impact of IDO inhibition during sepsis. Based on the available information one can speculate higher plasma levels of kynurenine during sepsis can promote the generation of iTregs that cause immunosuppression/immunoparalysis observed later in sepsis.

Additionally, human Tregs express an increased number of genes responsible for glycolysis than FAO *ex vivo* (Chapman et al., 2017; Procaccini et al., 2016). Upon activation, both Tregs and iTregs upregulate both FAO and glycolysis *ex vivo* (Procaccini et al., 2016). Both glycolysis and FAO are important for the maintenance of effective OXPHOS in both natural Tregs and iTregs (De Rosa et al., 2015; Procaccini et al., 2016) (Figure 2). An inhibition of glycolysis by 2-DG causes a decreased expression of CD25 on iTregs, while $CD25^{high}$ iTregs exhibit lesser immunosuppressive action due to lower expression of FOXP3 and activated STAT5 (De Rosa et al., 2017; Galgani et al., 2016; Procaccini et al., 2016). An inhibition of glycolysis causes binding of enolase-1 to the CNS2 promoter region of the FOXP3 exon 2 splice variant (FOXP3-E2) in human iTregs that further suppresses FOXP3-E2 expression required for immunosuppressive action of iTregs (De Rosa et al., 2015). Thus, both glucose or fatty-acid derived α-ketoglutaric acid (α-KG) has a potential to increase the expression of Treg signature via epigenetic regulation. Furthermore an acquisition of the glycolytic program plays a critical role in the immunosuppressive action of Tregs. However, deletion of GLUT1 does not have any impact on Treg differentiation and function (Macintyre et al., 2014).

HIF-1α upregulates glycolysis in macrophages and DCs and their pro-inflammatory phenotype (Cramer et al., 2003). However it slows down the differentiation of iTregs (Fig. 2) and enhances the differentiation of Th17 cells (Shi et al., 2011). HIF-1α also inhibits iTreg differentiation by causing the degradation of FOXP3 transcription factor through ubiquitin-proteasome-mediated degradation (Dang et al., 2011) (Fig. 2). Thus, glycolytic metabolites or regulators (i.e. HIF-1α) may impact various downstream signaling pathways required for immunosuppressive action of Tregs. In addition to glycolysis and FAO, a low level of mTOR signaling is also

required for proliferation and function of Tregs as indicated by higher mTORC1 signaling in Tregs (Procaccini et al., 2010; Zeng et al., 2013). But hyperactivation of mTORC1 proves detrimental to Tregs via increasing their ability to produce Th17 and Th1 cytokines (Park et al., 2013; Wei et al., 2016). Thus, mTORC1 signaling is crucially required for effective glycolysis and OXPHOS in Tregs as cholesterol and lipid biosynthesis induced downstream signaling of mTORC1 effectively controls Treg function (Chapman et al., 2017) (Fig. 2). This action of mTORC1 is induced via mevalonic acid/mevalonate-dependent lipid and cholesterol synthesis programs that support the growth and proliferation of Tregs (Chapman et al., 2017; Newton et al., 2016; Zeng et al., 2013). Both these pathways are involved in Treg proliferation and upregulation of cytotoxic T-lymphocyte associated antigen 4 (CTLA4) or CD152 and Inducible T-cell COStimulator (ICOS) or CD278 (Zeng et al., 2013). However mTORC1 does not directly impact the expression of FoxP3 in Tregs but inhibits mTORC2 and serves as major 'rheostat' for linking their immunological signals (Zeng et al., 2013).

PPAR signaling that drives FA uptake via CD36 and other FAO-related activities plays an essential role in adipose tissue-resident Tregs but not for splenic Treg function (Ahmadian et al., 2013; Cipolletta et al., 2012). PPAR signaling is shown to play an important role in the pathogenesis of sepsis and its outcome (von Knethen et al., 2007; Zingarelli and Cook, 2005). For example, decreased PPAR-α activity and its expression accounts for an increased mortality among mice subjected to sepsis (Standage et al., 2012). Furthermore, PPAR-β/δ signaling proves beneficial to mice subjected to LPS-induced endotoxemia or CLP-induced polymicrobial sepsis as PPAR-$\beta/\delta^{-/-}$ mice succumbed to sepsis earlier than WT mice (Kapoor et al., 2010; Zingarelli et al., 2010). While stimulation of PPAR-β/δ signaling via its agonist GW0742 protected septic mice through an increased phosphorylation of Akt and glycogen synthase kinase (GSK)-3β (Kapoor et al., 2010). In addition to PPAR-β/δ signaling, a defective PPAR-γ signaling is also observed in peripheral blood monocytes (PBMCs) of children affected with sepsis (Kaplan et al., 2010). Even PPAR-γ agonists are considered as novel therapeutics for pediatric sepsis (Kaplan and Zingarelli, 2011). Thus, PPAR signaling plays an important role in the sepsis pathogenesis and its outcome. Expression of PPARs by Tregs and its involvement in FAO and glycolysis in Tregs provides an opportunity to study this signaling in Tregs in context to sepsis. PPAR signalling-mediated protective action also depends on an increased phosphorylation of Akt and GSK-3β, both are required for effective glycolysis and pro-inflammatory action in myeloid cells (Kelly and O'Neill, 2015) but their role in Tregs during sepsis needs to be investigated potentially.

Leptin is shown to affect both innate and adaptive immune cells and immunological diseases including autoimmunity (Fernandez-Riejos et al., 2010; Procaccini et al., 2017; Procaccini et al., 2015). Leptin-associated nutritional status of the host with pro-inflammatory Th1 immune responses and its decreased plasma levels during food deprivation or other high energy demanding conditions like sepsis may cause an impairment in immune response (Procaccini et al., 2015). Tregs constitutively express leptin receptor (LEPR, also called OBR) and also produce leptin during normal conditions and upon their activation (Chapman et al., 2017). Leptin-LEPR signaling increases mTORC1 signaling in Tregs and inhibits their proliferation (Chapman et al., 2017). Thus, suppression of leptin-LEPR signaling in Tregs causes an increase in their proliferation as observed with the treatment with rapamycin, an mTOR inhibitor (Procaccini et al., 2010). Interestingly, an increased serum level of leptin is observed in critically ill patients suffering from sepsis as early as the second day of admission in ICU (Bracho-Riquelme and Reyes-Romero, 2010; Yousef et al., 2010).

An increased serum levels of leptin and soluble leptin receptor (sLR) are well associated with increased mortality among animals and patients suffering from sepsis (Shapiro et al., 2010). Additionally, exogenous leptin in animals with CLP-induced sepsis also increases their mortality (Shapiro et al., 2010). However, its level decreases in prolonged cases of sepsis (Tzanela et al., 2006). Its serum levels can be used independently to predict the development of sepsis and its outcome in patients (Jacobsson et al., 2017). Thus, it will be interesting to study the impact of leptin on Tregs isolated from septic patients as higher serum levels of leptin are observed in early phase of sepsis. At this stage binding of leptin to LEPR expressed on Tregs can cause an increased mTORC1 signaling. This increased mTORC1 signaling may cause an inhibition of proliferation and immunosuppressive function of Tregs. Furthermore, decreased levels of leptin during later stages of sepsis may impact Tregs as their will not be enough circulating leptin to stimulate leptin-LEPR axis on Tregs required for activation of mTORC1 signaling to inhibit their proliferation. Thus, this situation causes an increased immunosuppression as observed in later cases of sepsis making these patients more susceptible to secondary infections and death. This immunoregulatory axis of leptin-LEPR axis on Tregs during both at early and late stages of sepsis is urgently needed to be studied.

4. Targeting T cells/Tregs and their immunometabolism in sepsis

T cell immunometabolism has been well studied in context to cancer and autoimmunity [i.e. systemic lupus erythematosus (SLE)] (Benke et al., 1991; Biswas, 2015; Gergely et al., 2002;

Kouidhi et al., 2017; Luo et al., 2017). Despite different origin and pathogenesis cancer and sepsis induce similar devastating impact on immune response that certain observations made in sepsis can easily be transferred to cancer and vice versa (Dyck and Mills, 2017; Hotchkiss and Moldawer, 2014). Hence an emerging role of conventional T cells and Tregs in the pathogenesis of sepsis also provides a clue to target these cells and their immunometabolism. Thus, strategies to target sepsis should not be based on just targeting innate immune system but should also be focused on cells of adaptive immunity (i.e. T cells and their immunometabolism). For example acute infections causing sepsis are shown to inhibit FAO (Feingold et al., 2009). While FAO and OXPHOS are the major sources of ATP for both conventional T cell and Tregs. This impact of acute infection on these cells needed to be considered for future sepsis research.

Sepsis/tumor environment are so severe conditions that conventional T cells along with other innate immune cells (i.e. monocytes/macrophages, neutrophils and DCs) undergo apoptotic cell death and cause immunosuppression (Scharping et al., 2016). And this immunosuppression is further aggravated by Tregs that act as potent immunosuppressive cells. Tregs have a unique property to survive the harsh environment generated by sepsis causing immunosuppression that lasts even after recovering from sepsis (Cavassani et al., 2010). This is because transcription factor FoxP3 reprograms the metabolic stage (i.e. mTORC1 signaling, glucose metabolism and OXPHOS) of these cells in such a way that they maintain their immunosuppressive functions in low glucose and high lactate concentration environment (Angelin et al., 2017; Gerriets et al., 2016; Howie et al., 2017) (Fig. 2). Thus targeting Treg immunometabolism during sepsis will provide novel therapeutic approach. Furthermore, strategies used to upregulate the effector function of Tregs at early pro-inflammatory condition during sepsis may prove helpful to dampen exaggerated systemic inflammation and organ damage. For example, Celastrol, a Chinese herbal compound has shown promising results in this direction where an early induction of Tregs in rheumatoid arthritis (RA) prevented exaggerated joint inflammation and tissue damage (Astry et al., 2015). In addition, this compound also has direct impact on LPS-TLR4 interaction, a major pro-inflammatory mechanism responsible gram-negative bacterial sepsis (Lee et al., 2015b).

Another approach in this direction may comprise of reprogramming of other pro-inflammatory cells at early stages of sepsis into Tregs. A step in this direction has been taken where inhibition of 2-hydroxyglutarate synthesis by small molecule,(aminooxy)acetic acid skewed pro-inflammatory Th17 into Tregs (Xu et al., 2017). This is because accumulation of

2-hydroxyglutarate inhibits FoxP3 via hypermethylation of *Foxp3* gene. The selective inhibition of GOT1 with (aminooxy)acetic acid prevents an increased transamination responsible for the generation of 2-hydroxyglutarate through the conversion of glutamate to α-KG (Xu et al., 2017). Targeting a glutamate-dependent metabolic pathway in inflammatory conditions associated with an imbalance between Th17 cell and Tregs may prove a novel therapeutic strategy to control an exaggerated inflammation (Sun et al., 2017). Sepsis and associated acute respiratory distress syndrome (ARDS) are also considered a situation of imbalance between Th17 and Tregs (Guo et al., 2017; Yu et al., 2015b). An injection of a Chinese herbal medicine called Xuebijing (XBJ) containing extracts from 5 herbs potentially improved the survival of animals subjected to polymicrobial sepsis and septic shock (Chen et al., 2018). This protective effects involves the prevention of generation of cytokine storm, exaggerated inflammation along with regulating the balance between Tregs and Th17 cells (Chen et al., 2018).

Additionally an inhibition of glutamine metabolism by using specific antagonist called 6-Diazo-5-oxoL-norleucine or DON in mouse model of cerebral malaria and viral encephalitis increased the survival (Gordon et al., 2015; Manivannan et al., 2016). A combination of DON, 2-DG (a glycolysis inhibitor) and metformin (an antidiabetic drug that inhibits mitochondrial complex I and promotes FAO) significantly inhibited $CD4^+$ and $CD8^+$ T cell effector response (Patel and Powell, 2017). This combined therapy reciprocally enhances the generation of antigen-specific Tregs due to different immunometabolic demands of these cells (Patel and Powell, 2017). In animal models of allograft skin and heart transplantation, this metabolic therapy significantly proved beneficial and promoted allograft acceptance (Patel and Powell, 2017). Future studies in this direction have great potential to provide beneficial therapeutic approach to target sepsis.

The activation of Tregs during several infectious and inflammatory conditions has shown that their immunosuppressive action also involves the suppression of pro-inflammatory innate immune response (Antunes and Kassiotis, 2010; Kinsey et al., 2009). Thus strategies that can be used to target immunometabolism of conventional T cells during early inflammatory stage of sepsis can prove helpful to target overwhelming inflammation. For example, rapamycin, an inhibitor of mTOR signaling that controls glycolysis, FA synthesis and mitochondrial biogenesis is shown to promote Treg generation (Battaglia et al., 2005; Patel and Powell, 2017; Waickman and Powell, 2012). Thus this property of rapamycin can be used to investigate its effect on Tregs during early stages of sepsis to counteract the exaggerated pro-inflammatory

immune response. For example, rapamycin is shown to inhibit LPS-induced acute lung injury (ALI) by attenuating the differentiation of Th17 cells producing pro-inflammatory cytokines to chemo-attract neutrophils towards the site of inflammation (Yan et al., 2016). This effect of rapamycin is mediated by the activation of SOCS3 and Gfi1, which further inhibit RORγt and STAT3 function (Yan et al., 2016). Another study has shown the protective action of rapamycin in sepsis-induced ALI in mice (Yen et al., 2013). Rapamycin is also shown to exert its protective action on sepsis-induced cognitive impairment in mice (Liu et al., 2017). However, impact of rapamycin on Tregs in these models of sepsis at different stages requires a specific attention in terms of future research to target Tregs.

Another enzyme of potential importance controlling pyruvate metabolism is pyruvate dehydrogenase (PDH) that converts pyruvate/pyruvic acid into acetyl co-A (Gerriets et al., 2015; Patel and Powell, 2017). The phosphorylation of PDH by PDH kinase (PDHK) causes its inhibition (Patel and Powell, 2017). Inhibition of PDHK provides an opportunity to generate the population of Tregs with an increased OXPHOS that can dampen an overwhelming pro-inflammatory immune response during early stages of sepsis/inflammation (Patel and Powell, 2017). The target of PDHK1 with dichloroacetate (DCA) in mice have significantly decreased the inflammation associated with experimental autoimmune encephalitis (EAE) (Gerriets et al., 2015).

In addition to direct enzymes or proteins controlling Treg function different vitamins including vitamins A, D, B_3 and B_9 also influence their biology and function (Wawman et al., 2017; Zeng and Chi, 2015). Reports are available and confirming that vitamin D supplementation potentially increases percentage of Tregs in healthy individuals (Prietl et al., 2010). Vitamin D deficiency is well associated with the different autoimmune diseases including multiple sclerosis (MS), inflammatory bowel disease (IBD) and cancer (Ardesia et al., 2015; Garland et al., 2006; Mocanu et al., 2013). However a recent report has also shown a strong association between vitamin D deficiency and an increased susceptibility to sepsis (Upala et al., 2015). Further studies have indicated that vitamin D deficiency in critically ill patients prior to their hospital admission serves as an important predictor of sepsis (de Haan et al., 2014; Moromizato et al., 2014). A more recent study has shown that a vitamin D deficiency upon ICU admission does not increases mortality with severe sepsis and septic shock but these patients more frequently exhibit diabetes, develop hospital-acquired infections and more frequently develop acute kidney injury (AKI) as compared to patients with normal vitamin D levels (Ala-Kokko et al., 2016). An increased pro-inflammatory immune response during

sepsis and increased bacterial load in circulation and lungs is obeserved in animals deficient in vitamin D (Parekh et al., 2017). A randomized controlled trial has shown that calcitriol or vitamin D supplementation exerted some immunomodulatory action that are needed to confirm by an additional phase II trial (Leaf et al., 2014; Quraishi et al., 2015). Another study has indicated the protective effect of vitamins and hydrocortisone supplementation on sepsis and septic shock associated organ damage including AKI and mortality (Marik et al., 2017). Thus, it would be interesting to observe the effect of vitamin D supplementation on conventional T cells and Tregs and their immunometabolism during sepsis as studies have indicated the impact of vitamin D supplementation on conventional $CD4^+$ T cells in human (Konijeti et al., 2016).

5. Conclusion

Sepsis is a very devastating health care problem with its increased prevalence all over the world and proved economic burden. It affects both body's basal metabolism and energy requirement with an impact on immunometabolic pathways of body's immune cells. T cells are the potential cells of the adaptive immune system that gained their importance in sepsis due to their apoptotic cell death during early stages of sepsis and marked immunoparalysis/immunosuppression in its later stages. A marked alteration in their immunometabolic stage during sepsis is discussed extensively here along with various therapeutic approaches to target these cells and their immunometabolism during sepsis. Additionally, an increased ROS level is observed in the peripheral blood of the patients during early stages of sepsis (Oliveira et al., 2017). Thus, it will be interesting to observe the impact of increased systemic ROS levels on the $CD4^+$, $CD8^+$, and $CD4^+CD8^+$ T cells and their immunometabolism during early sepsis. For example, ROS–associated molecular signature have been targeted recently as biomarkers to define mortality or predict survival among sepsis patients (Bime et al., 2016). Mitochondrial dysfunction and oxidative stress are well correlated with sepsis-associated organ damage (Galley, 2011; Rocha et al., 2012). Thus, antioxidant therapies targeting mitochondria can be used to target specifically different subsets of T cells during different stages of sepsis as a specific cellular therapeutic approach. Hence, targeting T cells immunometabolism either at early stage of sepsis or during the late stage of sepsis has great therapeutic potential. Additionally, recent study has shown the reprogramming of B cells into T cells via a transcription factor called Hoxb5 (Zhang et al., 2018). This approach can be utilized to target sepsis-associated immunosuppression. Thus the area of T cell immunometabolism associated with sepsis also needs greater attention along with other inflammatory conditions including cancer and

autoimmunity. Additionally, targeting T cells and their metabolism will provide a new direction in the field of precision medicine based on immunomodulation during sepsis.

Declaration of Interest:

Nothing to declare.

References:

Ahmadian, M., Suh, J.M., Hah, N., Liddle, C., Atkins, A.R., Downes, M., Evans, R.M., 2013. PPARgamma signaling and metabolism: the good, the bad and the future. Nature medicine 19, 557-566.
Ala-Kokko, T.I., Mutt, S.J., Nisula, S., Koskenkari, J., Liisanantti, J., Ohtonen, P., Poukkanen, M., Laurila, J.J., Pettila, V., Herzig, K.H., 2016. Vitamin D deficiency at admission is not associated with 90-day mortality in patients with severe sepsis or septic shock: Observational FINNAKI cohort study. Annals of medicine 48, 67-75.
Almeida, L., Lochner, M., Berod, L., Sparwasser, T., 2016. Metabolic pathways in T cell activation and lineage differentiation. Seminars in immunology 28, 514-524.
Andreu-Ballester, J.C., Cuellar, C., Garcia-Ballesteros, C., Perez-Griera, J., Amigo, V., Peiro-Gomez, A., Penarroja-Otero, C., Ballester, F., Mayans, J., Tormo-Calandin, C., 2014. Deficit of interleukin 7 in septic patients. International immunopharmacology 23, 73-76.
Angelin, A., Gil-de-Gomez, L., Dahiya, S., Jiao, J., Guo, L., Levine, M.H., Wang, Z., Quinn, W.J., 3rd, Kopinski, P.K., Wang, L., Akimova, T., Liu, Y., Bhatti, T.R., Han, R., Laskin, B.L., Baur, J.A., Blair, I.A., Wallace, D.C., Hancock, W.W., Beier, U.H., 2017. Foxp3 Reprograms T Cell Metabolism to Function in Low-Glucose, High-Lactate Environments. Cell metabolism 25, 1282-1293.e1287.
Antunes, I., Kassiotis, G., 2010. Suppression of Innate Immune Pathology by Regulatory T Cells during Influenza A Virus Infection of Immunodeficient Mice. Journal of virology 84, 12564-12575.
Arce-Sillas, A., #xc1, lvarez-Luqu, #xed, n, D.D., Tamaya-Dom, #xed, nguez, B., Gomez-Fuentes, S., Trejo-Garc, #xed, a, A., Melo-Salas, M., #xe1, rdenas, G., Rodr, #xed, guez-Ram, #xed, rez, J., Adalid-Peralta, L., 2016. Regulatory T Cells: Molecular Actions on Effector Cells in Immune Regulation. Journal of Immunology Research 2016, 12.
Ardesia, M., Ferlazzo, G., Fries, W., 2015. Vitamin D and Inflammatory Bowel Disease. BioMed research international 2015, 470805.
Asadzadeh, Z., Mohammadi, H., Safarzadeh, E., Hemmatzadeh, M., Mahdian-Shakib, A., Jadidi-Niaragh, F., Azizi, G., Baradaran, B., 2017. The paradox of Th17 cell functions in tumor immunity. Cellular immunology 322, 15-25.
Astry, B., Venkatesha, S.H., Laurence, A., Christensen-Quick, A., Garzino-demo, A., Frieman, M.B., O'Shea, J.J., Moudgil, K.D., 2015. Celastrol, a Chinese herbal compound, controls autoimmune inflammation by altering the balance of pathogenic and regulatory T cells in the target organ. Clinical Immunology 157, 228-238.
Bacchetta, R., Passerini, L., Gambineri, E., Dai, M., Allan, S.E., Perroni, L., Dagna-Bricarelli, F., Sartirana, C., Matthes-Martin, S., Lawitschka, A., Azzari, C., Ziegler, S.F., Levings, M.K., Roncarolo, M.G., 2006.

Defective regulatory and effector T cell functions in patients with FOXP3 mutations. The Journal of clinical investigation 116, 1713-1722.
Bailey, S.R., Nelson, M.H., Himes, R.A., Li, Z., Mehrotra, S., Paulos, C.M., 2014. Th17 Cells in Cancer: The Ultimate Identity Crisis. Frontiers in immunology 5, 276.
Bantug, G.R., Galluzzi, L., Kroemer, G., Hess, C., 2018. The spectrum of T cell metabolism in health and disease. Nature reviews. Immunology 18, 19-34.
Battaglia, M., Stabilini, A., Roncarolo, M.G., 2005. Rapamycin selectively expands CD4+CD25+FoxP3+ regulatory T cells. Blood 105, 4743-4748.
Bauer, M., Giamarellos-Bourboulis, E.J., Kortgen, A., Moller, E., Felsmann, K., Cavaillon, J.M., Guntinas-Lichius, O., Rutschmann, O., Ruryk, A., Kohl, M., Wlotzka, B., Russwurm, S., Marshall, J.C., Reinhart, K., 2016. A Transcriptomic Biomarker to Quantify Systemic Inflammation in Sepsis - A Prospective Multicenter Phase II Diagnostic Study. EBioMedicine 6, 114-125.
Beier, U.H., Angelin, A., Akimova, T., Wang, L., Liu, Y., Xiao, H., Koike, M.A., Hancock, S.A., Bhatti, T.R., Han, R., Jiao, J., Veasey, S.C., Sims, C.A., Baur, J.A., Wallace, D.C., Hancock, W.W., 2015. Essential role of mitochondrial energy metabolism in Foxp3(+) T-regulatory cell function and allograft survival. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 29, 2315-2326.
Belkaid, Y., Rouse, B.T., 2005. Natural regulatory T cells in infectious disease. Nature immunology 6, 353-360.
Benke, P.J., Drisko, J., Ahmad, P., 1991. Increased oxidative metabolism in phytohemagglutinin-stimulated lymphocytes from patients with systemic lupus erythematosus is associated with serum SSA antibody. Biochemical medicine and metabolic biology 45, 28-40.
Bennett, C.L., Christie, J., Ramsdell, F., Brunkow, M.E., Ferguson, P.J., Whitesell, L., Kelly, T.E., Saulsbury, F.T., Chance, P.F., Ochs, H.D., 2001. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nature Genetics 27, 20.
Berod, L., Friedrich, C., Nandan, A., Freitag, J., Hagemann, S., Harmrolfs, K., Sandouk, A., Hesse, C., Castro, C.N., Bahre, H., Tschirner, S.K., Gorinski, N., Gohmert, M., Mayer, C.T., Huehn, J., Ponimaskin, E., Abraham, W.R., Muller, R., Lochner, M., Sparwasser, T., 2014. De novo fatty acid synthesis controls the fate between regulatory T and T helper 17 cells. Nature medicine 20, 1327-1333.
Best, J.A., Blair, D.A., Knell, J., Yang, E., Mayya, V., Doedens, A., Dustin, M.L., Goldrath, A.W., 2013. Transcriptional insights into the CD8(+) T cell response to infection and memory T cell formation. Nature immunology 14, 404-412.
Bime, C., Zhou, T., Wang, T., Slepian, M.J., Garcia, J.G.N., Hecker, L., 2016. Reactive oxygen species–associated molecular signature predicts survival in patients with sepsis. Pulmonary Circulation 6, 196-201.
Binger, K.J., Côrte-Real, B.F., Kleinewietfeld, M., 2017. Immunometabolic Regulation of Interleukin-17-Producing T Helper Cells: Uncoupling New Targets for Autoimmunity. Frontiers in immunology 8, 311.
Biswas, S.K., 2015. Metabolic Reprogramming of Immune Cells in Cancer Progression. Immunity 43, 435-449.
Blagih, J., Coulombe, F., Vincent, E.E., Dupuy, F., Galicia-Vazquez, G., Yurchenko, E., Raissi, T.C., van der Windt, G.J., Viollet, B., Pearce, E.L., Pelletier, J., Piccirillo, C.A., Krawczyk, C.M., Divangahi, M., Jones, R.G., 2015. The energy sensor AMPK regulates T cell metabolic adaptation and effector responses in vivo. Immunity 42, 41-54.
Bluestone, J.A., Bour-Jordan, H., Cheng, M., Anderson, M., 2015. T cells in the control of organ-specific autoimmunity. The Journal of clinical investigation 125, 2250-2260.
Boomer, J.S., To, K., Chang, K.C., Takasu, O., Osborne, D.F., Walton, A.H., Bricker, T.L., Jarman, S.D., 2nd, Kreisel, D., Krupnick, A.S., Srivastava, A., Swanson, P.E., Green, J.M., Hotchkiss, R.S., 2011. Immunosuppression in patients who die of sepsis and multiple organ failure. Jama 306, 2594-2605.
Bosmann, M., Ward, P.A., 2013. The inflammatory response in sepsis. Trends in immunology 34, 129-136.

Botero, J.S.n.H.n., Pérez, M.a.C.F.n., 2012. The History of Sepsis from Ancient Egypt to the XIX Century, in: Azevedo, L. (Ed.), Sepsis - An Ongoing and Significant Challenge. InTech, Rijeka, p. Ch. 01.
Bracho-Riquelme, R.L., Reyes-Romero, M.A., 2010. Leptin in sepsis: a well-suited biomarker in critically ill patients? Critical Care 14, 138-138.
Brucklacher-Waldert, V., Steinbach, K., Lioznov, M., Kolster, M., Holscher, C., Tolosa, E., 2009. Phenotypical characterization of human Th17 cells unambiguously identified by surface IL-17A expression. Journal of immunology (Baltimore, Md. : 1950) 183, 5494-5501.
Brunialti, M.K., Santos, M.C., Rigato, O., Machado, F.R., Silva, E., Salomao, R., 2012. Increased percentages of T helper cells producing IL-17 and monocytes expressing markers of alternative activation in patients with sepsis. PloS one 7, e37393.
Buck, M.D., O'Sullivan, D., Pearce, E.L., 2015. T cell metabolism drives immunity. The Journal of experimental medicine 212, 1345-1360.
Buck, M.D., Sowell, R.T., Kaech, S.M., Pearce, E.L., 2017. Metabolic Instruction of Immunity. Cell 169, 570-586.
Cabrera-Perez, J., Condotta, S.A., Badovinac, V.P., Griffith, T.S., 2014. Impact of sepsis on CD4 T cell immunity. Journal of leukocyte biology 96, 767-777.
Cao, C., Ma, T., Chai, Y.F., Shou, S.T., 2015. The role of regulatory T cells in immune dysfunction during sepsis. World journal of emergency medicine 6, 5-9.
Cao, Y., Rathmell, J.C., Macintyre, A.N., 2014. Metabolic reprogramming towards aerobic glycolysis correlates with greater proliferative ability and resistance to metabolic inhibition in CD8 versus CD4 T cells. PloS one 9, e104104.
Carson, W.F.t., Cavassani, K.A., Ito, T., Schaller, M., Ishii, M., Dou, Y., Kunkel, S.L., 2010. Impaired CD4+ T-cell proliferation and effector function correlates with repressive histone methylation events in a mouse model of severe sepsis. European journal of immunology 40, 998-1010.
Cavassani, K.A., Carson, W.F.t., Moreira, A.P., Wen, H., Schaller, M.A., Ishii, M., Lindell, D.M., Dou, Y., Lukacs, N.W., Keshamouni, V.G., Hogaboam, C.M., Kunkel, S.L., 2010. The post sepsis-induced expansion and enhanced function of regulatory T cells create an environment to potentiate tumor growth. Blood 115, 4403-4411.
Changsirivathanathamrong, D., Wang, Y., Rajbhandari, D., Maghzal, G.J., Mak, W.M., Woolfe, C., Duflou, J., Gebski, V., dos Remedios, C.G., Celermajer, D.S., Stocker, R., 2011. Tryptophan metabolism to kynurenine is a potential novel contributor to hypotension in human sepsis. Critical care medicine 39, 2678-2683.
Chapman, N.M., Shrestha, S., Chi, H., 2017. Metabolism in Immune Cell Differentiation and Function. Advances in experimental medicine and biology 1011, 1-85.
Chen, X., Feng, Y., Shen, X., Pan, G., Fan, G., Gao, X., Han, J., Zhu, Y., 2018. Anti-sepsis protection of Xuebijing injection is mediated by differential regulation of pro- and anti-inflammatory Th17 and T regulatory cells in a murine model of polymicrobial sepsis. J Ethnopharmacol 211, 358-365.
Cheng, S.C., Scicluna, B.P., Arts, R.J., Gresnigt, M.S., Lachmandas, E., Giamarellos-Bourboulis, E.J., Kox, M., Manjeri, G.R., Wagenaars, J.A., Cremer, O.L., Leentjens, J., van der Meer, A.J., van de Veerdonk, F.L., Bonten, M.J., Schultz, M.J., Willems, P.H., Pickkers, P., Joosten, L.A., van der Poll, T., Netea, M.G., 2016. Broad defects in the energy metabolism of leukocytes underlie immunoparalysis in sepsis. Nature immunology 17, 406-413.
Chi, H., 2012. Regulation and function of mTOR signalling in T cell fate decisions. Nature reviews. Immunology 12, 325-338.
Chou, C., Pinto, A.K., Curtis, J.D., Persaud, S.P., Cella, M., Lin, C.C., Edelson, B.T., Allen, P.M., Colonna, M., Pearce, E.L., Diamond, M.S., Egawa, T., 2014. c-Myc-induced transcription factor AP4 is required for host protection mediated by CD8+ T cells. Nature immunology 15, 884-893.
Chou, C., Verbaro, D.J., Tonc, E., Holmgren, M., Cella, M., Colonna, M., Bhattacharya, D., Egawa, T., 2016. The Transcription Factor AP4 Mediates Resolution of Chronic Viral Infection through Amplification of Germinal Center B Cell Responses. Immunity 45, 570-582.

Cipolletta, D., Feuerer, M., Li, A., Kamei, N., Lee, J., Shoelson, S.E., Benoist, C., Mathis, D., 2012. PPAR-gamma is a major driver of the accumulation and phenotype of adipose tissue Treg cells. Nature 486, 549-553.

Clever, D., Roychoudhuri, R., Constantinides, M.G., Askenase, M.H., Sukumar, M., Klebanoff, C.A., Eil, R.L., Hickman, H.D., Yu, Z., Pan, J.H., Palmer, D.C., Phan, A.T., Goulding, J., Gattinoni, L., Goldrath, A.W., Belkaid, Y., Restifo, N.P., 2016. Oxygen Sensing by T Cells Establishes an Immunologically Tolerant Metastatic Niche. Cell 166, 1117-1131.e1114.

Coe, D.J., Kishore, M., Marelli-Berg, F., 2014. Metabolic regulation of regulatory T cell development and function. Frontiers in immunology 5, 590.

Condotta, S.A., Cabrera-Perez, J., Badovinac, V.P., Griffith, T.S., 2013. T-cell mediated immunity and the role of TRAIL in sepsis-induced immunosuppression. Critical reviews in immunology 33, 23-40.

Cramer, T., Yamanishi, Y., Clausen, B.E., Forster, I., Pawlinski, R., Mackman, N., Haase, V.H., Jaenisch, R., Corr, M., Nizet, V., Firestein, G.S., Gerber, H.P., Ferrara, N., Johnson, R.S., 2003. HIF-1alpha is essential for myeloid cell-mediated inflammation. Cell 112, 645-657.

Danahy, D.B., Strother, R.K., Badovinac, V.P., Griffith, T.S., 2016. Clinical and Experimental Sepsis Impairs CD8 T-Cell-Mediated Immunity. Critical reviews in immunology 36, 57-74.

Dang, E.V., Barbi, J., Yang, H.Y., Jinasena, D., Yu, H., Zheng, Y., Bordman, Z., Fu, J., Kim, Y., Yen, H.R., Luo, W., Zeller, K., Shimoda, L., Topalian, S.L., Semenza, G.L., Dang, C.V., Pardoll, D.M., Pan, F., 2011. Control of T(H)17/T(reg) balance by hypoxia-inducible factor 1. Cell 146, 772-784.

Darcy, C.J., Davis, J.S., Woodberry, T., McNeil, Y.R., Stephens, D.P., Yeo, T.W., Anstey, N.M., 2011. An Observational Cohort Study of the Kynurenine to Tryptophan Ratio in Sepsis: Association with Impaired Immune and Microvascular Function. PloS one 6, e21185.

Davies, S.P., Sim, A.T., Hardie, D.G., 1990. Location and function of three sites phosphorylated on rat acetyl-CoA carboxylase by the AMP-activated protein kinase. European journal of biochemistry 187, 183-190.

de Haan, K., Groeneveld, A.B., de Geus, H.R., Egal, M., Struijs, A., 2014. Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. Critical care (London, England) 18, 660.

De Rosa, V., Di Rella, F., Di Giacomo, A., Matarese, G., 2017. Regulatory T cells as suppressors of anti-tumor immunity: Role of metabolism. Cytokine & growth factor reviews 35, 15-25.

De Rosa, V., Galgani, M., Porcellini, A., Colamatteo, A., Santopaolo, M., Zuchegna, C., Romano, A., De Simone, S., Procaccini, C., La Rocca, C., Carrieri, P.B., Maniscalco, G.T., Salvetti, M., Buscarinu, M.C., Franzese, A., Mozzillo, E., La Cava, A., Matarese, G., 2015. Glycolysis controls the induction of human regulatory T cells by modulating the expression of FOXP3 exon 2 splicing variants. Nature immunology 16, 1174-1184.

Delano, M.J., Ward, P.A., 2016a. The immune system's role in sepsis progression, resolution, and long-term outcome. Immunological reviews 274, 330-353.

Delano, M.J., Ward, P.A., 2016b. Sepsis-induced immune dysfunction: can immune therapies reduce mortality? The Journal of clinical investigation 126, 23-31.

Delgoffe, G.M., Pollizzi, K.N., Waickman, A.T., Heikamp, E., Meyers, D.J., Horton, M.R., Xiao, B., Worley, P.F., Powell, J.D., 2011. The kinase mTOR regulates the differentiation of helper T cells through the selective activation of signaling by mTORC1 and mTORC2. Nature immunology 12, 295-303.

Diller, M.L., Kudchadkar, R.R., Delman, K.A., Lawson, D.H., Ford, M.L., 2016. Balancing Inflammation: The Link between Th17 and Regulatory T Cells. Mediators of inflammation 2016, 8.

Doedens, A.L., Phan, A.T., Stradner, M.H., Fujimoto, J.K., Nguyen, J.V., Yang, E., Johnson, R.S., Goldrath, A.W., 2013. Hypoxia-inducible factors enhance the effector responses of CD8(+) T cells to persistent antigen. Nature immunology 14, 1173-1182.

Dornmair, K., Goebels, N., Weltzien, H.-U., Wekerle, H., Hohlfeld, R., 2003. T-Cell-Mediated Autoimmunity: Novel Techniques to Characterize Autoreactive T-Cell Receptors. The American Journal of Pathology 163, 1215-1226.

Dyck, L., Mills, K.H.G., 2017. Immune checkpoints and their inhibition in cancer and infectious diseases. European journal of immunology 47, 765-779.
Esser, M.T., Bess, J.W., Jr., Suryanarayana, K., Chertova, E., Marti, D., Carrington, M., Arthur, L.O., Lifson, J.D., 2001. Partial activation and induction of apoptosis in CD4(+) and CD8(+) T lymphocytes by conformationally authentic noninfectious human immunodeficiency virus type 1. Journal of virology 75, 1152-1164.
Faubert, B., Boily, G., Izreig, S., Griss, T., Samborska, B., Dong, Z., Dupuy, F., Chambers, C., Fuerth, B.J., Viollet, B., Mamer, O.A., Avizonis, D., DeBerardinis, R.J., Siegel, P.M., Jones, R.G., 2013. AMPK is a negative regulator of the Warburg effect and suppresses tumor growth in vivo. Cell metabolism 17, 113-124.
Feingold, K.R., Moser, A., Patzek, S.M., Shigenaga, J.K., Grunfeld, C., 2009. Infection decreases fatty acid oxidation and nuclear hormone receptors in the diaphragm. Journal of lipid research 50, 2055-2063.
Fernandez-Riejos, P., Najib, S., Santos-Alvarez, J., Martin-Romero, C., Perez-Perez, A., Gonzalez-Yanes, C., Sanchez-Margalet, V., 2010. Role of leptin in the activation of immune cells. Mediators of inflammation 2010, 568343.
Ferreira, L.M., 2010. Cancer metabolism: the Warburg effect today. Experimental and molecular pathology 89, 372-380.
Figueiredo, M.M., Costa, P.A.C., Diniz, S.Q., Henriques, P.M., Kano, F.S., Tada, M.S., Pereira, D.B., Soares, I.S., Martins-Filho, O.A., Jankovic, D., Gazzinelli, R.T., Antonelli, L.R.d.V., 2017. T follicular helper cells regulate the activation of B lymphocytes and antibody production during Plasmodium vivax infection. PLOS Pathogens 13, e1006484.
Finfer, S., Machado, F.R., 2016. The Global Epidemiology of Sepsis. Does It Matter That We Know So Little? American journal of respiratory and critical care medicine 193, 228-230.
Fläring, U., Wernerman, J., Year Glutathione in Sepsis and Multiple Organ Failure. Berlin, Heidelberg.
Flaring, U.B., Rooyackers, O.E., Hebert, C., Bratel, T., Hammarqvist, F., Wernerman, J., 2005. Temporal changes in whole-blood and plasma glutathione in ICU patients with multiple organ failure. Intensive care medicine 31, 1072-1078.
Flaring, U.B., Rooyackers, O.E., Wernerman, J., Hammarqvist, F., 2003. Temporal changes in muscle glutathione in ICU patients. Intensive care medicine 29, 2193-2198.
Fleischmann, C., Scherag, A., Adhikari, N.K., Hartog, C.S., Tsaganos, T., Schlattmann, P., Angus, D.C., Reinhart, K., 2016. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. American journal of respiratory and critical care medicine 193, 259-272.
Fontenot, J.D., Rudensky, A.Y., 2005. A well adapted regulatory contrivance: regulatory T cell development and the forkhead family transcription factor Foxp3. Nature immunology 6, 331-337.
Franchina, D.G., Dostert, C., Brenner, D., 2018. Reactive Oxygen Species: Involvement in T Cell Signaling and Metabolism. Trends in immunology.
Funk, D.J., Parrillo, J.E., Kumar, A., 2009. Sepsis and septic shock: a history. Critical care clinics 25, 83-101, viii.
Galgani, M., De Rosa, V., La Cava, A., Matarese, G., 2016. Role of Metabolism in the Immunobiology of Regulatory T Cells. Journal of immunology (Baltimore, Md. : 1950) 197, 2567-2575.
Galley, H.F., 2011. Oxidative stress and mitochondrial dysfunction in sepsis. BJA: British Journal of Anaesthesia 107, 57-64.
Ganeshan, K., Chawla, A., 2014. Metabolic Regulation of Immune Responses. Annual Review of Immunology 32, 609-634.
Gao, R., Kan, M.Q., Wang, S.G., Yang, R.H., Zhang, S.G., 2016. Disrupted Tryptophan Metabolism Induced Cognitive Impairment in a Mouse Model of Sepsis-associated Encephalopathy. Inflammation 39, 550-560.
Garland, C.F., Garland, F.C., Gorham, E.D., Lipkin, M., Newmark, H., Mohr, S.B., Holick, M.F., 2006. The Role of Vitamin D in Cancer Prevention. American Journal of Public Health 96, 252-261.

Gergely, P., Jr., Grossman, C., Niland, B., Puskas, F., Neupane, H., Allam, F., Banki, K., Phillips, P.E., Perl, A., 2002. Mitochondrial hyperpolarization and ATP depletion in patients with systemic lupus erythematosus. Arthritis and rheumatism 46, 175-190.
Geroulanos, S., Douka, E.T., 2006. Historical perspective of the word "sepsis". Intensive care medicine 32, 2077.
Gerriets, V.A., Kishton, R.J., Johnson, M.O., Cohen, S., Siska, P.J., Nichols, A.G., Warmoes, M.O., de Cubas, A.A., MacIver, N.J., Locasale, J.W., Turka, L.A., Wells, A.D., Rathmell, J.C., 2016. Foxp3 and Toll-like receptor signaling balance Treg cell anabolic metabolism for suppression. Nature immunology 17, 1459-1466.
Gerriets, V.A., Kishton, R.J., Nichols, A.G., Macintyre, A.N., Inoue, M., Ilkayeva, O., Winter, P.S., Liu, X., Priyadharshini, B., Slawinska, M.E., Haeberli, L., Huck, C., Turka, L.A., Wood, K.C., Hale, L.P., Smith, P.A., Schneider, M.A., MacIver, N.J., Locasale, J.W., Newgard, C.B., Shinohara, M.L., Rathmell, J.C., 2015. Metabolic programming and PDHK1 control CD4+ T cell subsets and inflammation. The Journal of clinical investigation 125, 194-207.
Gordon, E.B., Hart, G.T., Tran, T.M., Waisberg, M., Akkaya, M., Kim, A.S., Hamilton, S.E., Pena, M., Yazew, T., Qi, C.F., Lee, C.F., Lo, Y.C., Miller, L.H., Powell, J.D., Pierce, S.K., 2015. Targeting glutamine metabolism rescues mice from late-stage cerebral malaria. Proc Natl Acad Sci U S A 112, 13075-13080.
Gorrini, C., Harris, I.S., Mak, T.W., 2013. Modulation of oxidative stress as an anticancer strategy. Nature reviews. Drug discovery 12, 931-947.
Guery, L., Hugues, S., 2015. Th17 Cell Plasticity and Functions in Cancer Immunity. BioMed research international 2015, 314620.
Guo, J., Tao, W., Tang, D., Zhang, J., 2017. Th17/regulatory T cell imbalance in sepsis patients with multiple organ dysfunction syndrome: attenuated by high-volume hemofiltration. The International journal of artificial organs 40, 607-614.
Healthcare, C., Utilization, P., 2008. HCUP Facts and Figures, HCUP Facts and Figures, 2006: Statistics on Hospital-Based Care in the United States. Agency for Healthcare Research and Quality (US), Rockville (MD).
Hein, F., Massin, F., Cravoisy-Popovic, A., Barraud, D., Levy, B., Bollaert, P.-E., Gibot, S., 2010. The relationship between CD4+CD25+CD127- regulatory T cells and inflammatory response and outcome during shock states. Critical Care 14, R19.
Hosac, A.M., 2002. Drotrecogin alfa (activated): the first FDA-approved treatment for severe sepsis. Proceedings (Baylor University. Medical Center) 15, 224-227.
Hotchkiss, R.S., Coopersmith, C.M., McDunn, J.E., Ferguson, T.A., 2009. The sepsis seesaw: tilting toward immunosuppression. Nature medicine 15, 496-497.
Hotchkiss, R.S., Moldawer, L.L., 2014. Parallels between cancer and infectious disease. The New England journal of medicine 371, 380-383.
Hotchkiss, R.S., Moldawer, L.L., Opal, S.M., Reinhart, K., Turnbull, I.R., Vincent, J.L., 2016. Sepsis and septic shock. Nature reviews. Disease primers 2, 16045.
Hotchkiss, R.S., Monneret, G., Payen, D., 2013. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. Nature reviews. Immunology 13, 862-874.
Hotchkiss, R.S., Swanson, P.E., Freeman, B.D., Tinsley, K.W., Cobb, J.P., Matuschak, G.M., Buchman, T.G., Karl, I.E., 1999a. Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. Critical care medicine 27, 1230-1251.
Hotchkiss, R.S., Swanson, P.E., Knudson, C.M., Chang, K.C., Cobb, J.P., Osborne, D.F., Zollner, K.M., Buchman, T.G., Korsmeyer, S.J., Karl, I.E., 1999b. Overexpression of Bcl-2 in transgenic mice decreases apoptosis and improves survival in sepsis. Journal of immunology (Baltimore, Md. : 1950) 162, 4148-4156.
Hotchkiss, R.S., Tinsley, K.W., Swanson, P.E., Schmieg, R.E., Jr., Hui, J.J., Chang, K.C., Osborne, D.F., Freeman, B.D., Cobb, J.P., Buchman, T.G., Karl, I.E., 2001. Sepsis-induced apoptosis causes progressive profound depletion of B and CD4+ T lymphocytes in humans. Journal of immunology (Baltimore, Md. : 1950) 166, 6952-6963.

Howie, D., Cobbold, S.P., Adams, E., Ten Bokum, A., Necula, A.S., Zhang, W., Huang, H., Roberts, D.J., Thomas, B., Hester, S.S., Vaux, D.J., Betz, A.G., Waldmann, H., 2017. Foxp3 drives oxidative phosphorylation and protection from lipotoxicity. JCI insight 2, e89160.

Hsu, P.P., Sabatini, D.M., 2008. Cancer cell metabolism: Warburg and beyond. Cell 134, 703-707.

Inoue, S., Suzuki-Utsunomiya, K., Okada, Y., Taira, T., Iida, Y., Miura, N., Tsuji, T., Yamagiwa, T., Morita, S., Chiba, T., Sato, T., Inokuchi, S., 2013. Reduction of immunocompetent T cells followed by prolonged lymphopenia in severe sepsis in the elderly. Critical care medicine 41, 810-819.

Jacobsson, S., Larsson, P., Johansson, G., Norberg, M., Wadell, G., Hallmans, G., Winsö, O., Söderberg, S., 2017. Leptin independently predicts development of sepsis and its outcome. Journal of Inflammation (London, England) 14, 19.

Jensen, I.J., Sjaastad, F.V., Griffith, T.S., Badovinac, V.P., 2018. Sepsis-Induced T Cell Immunoparalysis: The Ins and Outs of Impaired T Cell Immunity. The Journal of Immunology 200, 1543-1553.

Jensen, J.U., Bouadma, L., 2016. Why biomarkers failed in sepsis. Intensive care medicine 42, 2049-2051.

John, S., Weiss, J.N., Ribalet, B., 2011. Subcellular localization of hexokinases I and II directs the metabolic fate of glucose. PloS one 6, e17674.

Johnson, M.O., Siska, P.J., Contreras, D.C., Rathmell, J.C., 2016. Nutrients and the microenvironment to feed a T cell army. Seminars in immunology 28, 505-513.

Juno, J.A., van Bockel, D., Kent, S.J., Kelleher, A.D., Zaunders, J.J., Munier, C.M.L., 2017. Cytotoxic CD4 T Cells—Friend or Foe during Viral Infection? Frontiers in immunology 8, 19.

Kamiński, M.M., Röth, D., Sass, S., Sauer, S.W., Krammer, P.H., Gülow, K., 2012. Manganese superoxide dismutase: A regulator of T cell activation-induced oxidative signaling and cell death. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research 1823, 1041-1052.

Kaplan, J.M., Denenberg, A., Monaco, M., Nowell, M., Wong, H., Zingarelli, B., 2010. Changes in peroxisome proliferator activated receptor-gamma activity in children with septic shock. Intensive care medicine 36, 123-130.

Kaplan, J.M., Zingarelli, B., 2011. Novel Therapeutic Agents in Pediatric Sepsis: Peroxisome Proliferator Receptor γ (PPAR γ) Agonists. The open inflammation journal 4, 120-124.

Kapoor, A., Shintani, Y., Collino, M., Osuchowski, M.F., Busch, D., Patel, N.S., Sepodes, B., Castiglia, S., Fantozzi, R., Bishop-Bailey, D., Mota-Filipe, H., Yaqoob, M.M., Suzuki, K., Bahrami, S., Desvergne, B., Mitchell, J.A., Thiemermann, C., 2010. Protective role of peroxisome proliferator-activated receptor-beta/delta in septic shock. American journal of respiratory and critical care medicine 182, 1506-1515.

Karmaus, P.W., Chi, H., 2014. c-Myc and AP4: a relay team for metabolic reprogramming of CD8+ T cells. Nature immunology 15, 828-829.

Kastirr, I., Crosti, M., Maglie, S., Paroni, M., Steckel, B., Moro, M., Pagani, M., Abrignani, S., Geginat, J., 2015. Signal Strength and Metabolic Requirements Control Cytokine-Induced Th17 Differentiation of Uncommitted Human T Cells. Journal of immunology (Baltimore, Md. : 1950) 195, 3617-3627.

Kazi, A.A., Pruznak, A.M., Frost, R.A., Lang, C.H., 2011. Sepsis-induced alterations in protein-protein interactions within mTOR complex 1 and the modulating effect of leucine on muscle protein synthesis. Shock (Augusta, Ga.) 35, 117-125.

Keller, G.A., Barke, R., Harty, J.T., Humphrey, E., Simmons, R.L., 1985. Decreased hepatic glutathione levels in septic shock. Predisposition of hepatocytes to oxidative stress: an experimental approach. Archives of surgery (Chicago, Ill. : 1960) 120, 941-945.

Kelly, B., O'Neill, L.A.J., 2015. Metabolic reprogramming in macrophages and dendritic cells in innate immunity. Cell Research 25, 771-784.

Kessel, A., Bamberger, E., Masalha, M., Toubi, E., 2009. The role of T regulatory cells in human sepsis. Journal of autoimmunity 32, 211-215.

Kinsey, G.R., Sharma, R., Huang, L., Li, L., Vergis, A.L., Ye, H., Ju, S.-T., Okusa, M.D., 2009. Regulatory T Cells Suppress Innate Immunity in Kidney Ischemia-Reperfusion Injury. Journal of the American Society of Nephrology : JASN 20, 1744-1753.

Konijeti, G.G., Arora, P., Boylan, M.R., Song, Y., Huang, S., Harrell, F., Newton-Cheh, C., O'Neill, D., Korzenik, J., Wang, T.J., Chan, A.T., 2016. Vitamin D Supplementation Modulates T Cell–Mediated Immunity in Humans: Results from a Randomized Control Trial. The Journal of Clinical Endocrinology and Metabolism 101, 533-538.

Koppenol, W.H., Bounds, P.L., Dang, C.V., 2011. Otto Warburg's contributions to current concepts of cancer metabolism. Nature reviews. Cancer 11, 325-337.

Korn, T., Bettelli, E., Oukka, M., Kuchroo, V.K., 2009. IL-17 and Th17 Cells. Annu Rev Immunol 27, 485-517.

Kouidhi, S., Elgaaied, A.B., Chouaib, S., 2017. Impact of Metabolism on T-Cell Differentiation and Function and Cross Talk with Tumor Microenvironment. Frontiers in immunology 8, 270.

Kumar, V., Sharma, A., 2008. Innate immunity in sepsis pathogenesis and its modulation: new immunomodulatory targets revealed. Journal of chemotherapy (Florence, Italy) 20, 672-683.

Kurebayashi, Y., Nagai, S., Ikejiri, A., Ohtani, M., Ichiyama, K., Baba, Y., Yamada, T., Egami, S., Hoshii, T., Hirao, A., Matsuda, S., Koyasu, S., 2012. PI3K-Akt-mTORC1-S6K1/2 axis controls Th17 differentiation by regulating Gfi1 expression and nuclear translocation of RORgamma. Cell reports 1, 360-373.

Lai, D., Qin, C., Shu, Q., 2014. Myeloid-derived suppressor cells in sepsis. BioMed research international 2014, 598654.

Laplante, M., Sabatini, D.M., 2012. mTOR signaling in growth control and disease. Cell 149, 274-293.

Laufenberg, L.J., Pruznak, A.M., Navaratnarajah, M., Lang, C.H., 2014. Sepsis-induced changes in amino acid transporters and leucine signaling via mTOR in skeletal muscle. Amino acids 46, 2787-2798.

Leaf, D.E., Raed, A., Donnino, M.W., Ginde, A.A., Waikar, S.S., 2014. Randomized Controlled Trial of Calcitriol in Severe Sepsis. American journal of respiratory and critical care medicine 190, 533-541.

Lee, C.F., Lo, Y.C., Cheng, C.H., Furtmuller, G.J., Oh, B., Andrade-Oliveira, V., Thomas, A.G., Bowman, C.E., Slusher, B.S., Wolfgang, M.J., Brandacher, G., Powell, J.D., 2015a. Preventing Allograft Rejection by Targeting Immune Metabolism. Cell reports 13, 760-770.

Lee, J.Y., Lee, B.H., Kim, N.D., Lee, J.Y., 2015b. Celastrol blocks binding of lipopolysaccharides to a Toll-like receptor4/myeloid differentiation factor2 complex in a thiol-dependent manner. Journal of Ethnopharmacology 172, 254-260.

Liston, A., Enders, A., Siggs, O.M., 2008. Unravelling the association of partial T-cell immunodeficiency and immune dysregulation. Nature reviews. Immunology 8, 545-558.

Liu, W., Guo, J., Mu, J., Tian, L., Zhou, D., 2017. Rapamycin Protects Sepsis-Induced Cognitive Impairment in Mouse Hippocampus by Enhancing Autophagy. Cellular and molecular neurobiology 37, 1195-1205.

Lochner, M., Berod, L., Sparwasser, T., 2015. Fatty acid metabolism in the regulation of T cell function. Trends in immunology 36, 81-91.

Luo, X., Zhu, F., Chen, Z., Li, D., Li, B., 2017. Regulation of Metabolism Across Different Subsets of T Cells in Cancer. Advances in experimental medicine and biology 1011, 197-209.

Ma, E.H., Poffenberger, M.C., Wong, A.H., Jones, R.G., 2017. The role of AMPK in T cell metabolism and function. Current opinion in immunology 46, 45-52.

Ma, L., Zhang, H., Hu, K., Lv, G., Fu, Y., Ayana, D.A., Zhao, P., Jiang, Y., 2015. The imbalance between Tregs, Th17 cells and inflammatory cytokines among renal transplant recipients. BMC Immunology 16, 56.

Macintyre, A.N., Gerriets, V.A., Nichols, A.G., Michalek, R.D., Rudolph, M.C., Deoliveira, D., Anderson, S.M., Abel, E.D., Chen, B.J., Hale, L.P., Rathmell, J.C., 2014. The glucose transporter Glut1 is selectively essential for CD4 T cell activation and effector function. Cell metabolism 20, 61-72.

MacIver, N.J., Michalek, R.D., Rathmell, J.C., 2013. Metabolic regulation of T lymphocytes. Annu Rev Immunol 31, 259-283.

Maddur, M.S., Miossec, P., Kaveri, S.V., Bayry, J., 2012. Th17 cells: biology, pathogenesis of autoimmune and inflammatory diseases, and therapeutic strategies. Am J Pathol 181, 8-18.

Majno, G., 1991. The ancient riddle of sigma eta psi iota sigma (sepsis). The Journal of infectious diseases 163, 937-945.

Mak, T.W., Grusdat, M., Duncan, G.S., Dostert, C., Nonnenmacher, Y., Cox, M., Binsfeld, C., Hao, Z., Brustle, A., Itsumi, M., Jager, C., Chen, Y., Pinkenburg, O., Camara, B., Ollert, M., Bindslev-Jensen, C., Vasiliou, V., Gorrini, C., Lang, P.A., Lohoff, M., Harris, I.S., Hiller, K., Brenner, D., 2017. Glutathione Primes T Cell Metabolism for Inflammation. Immunity 46, 675-689.

Manivannan, S., Baxter, V.K., Schultz, K.L., Slusher, B.S., Griffin, D.E., 2016. Protective Effects of Glutamine Antagonist 6-Diazo-5-Oxo-l-Norleucine in Mice with Alphavirus Encephalomyelitis. Journal of virology 90, 9251-9262.

Maria, N.I., van Helden-Meeuwsen, C.G., Brkic, Z., Paulissen, S.M., Steenwijk, E.C., Dalm, V.A., van Daele, P.L., Martin van Hagen, P., Kroese, F.G., van Roon, J.A., Harkin, A., Dik, W.A., Drexhage, H.A., Lubberts, E., Versnel, M.A., 2016. Association of Increased Treg Cell Levels With Elevated Indoleamine 2,3-Dioxygenase Activity and an Imbalanced Kynurenine Pathway in Interferon-Positive Primary Sjogren's Syndrome. Arthritis & rheumatology (Hoboken, N.J.) 68, 1688-1699.

Marik, P.E., Khangoora, V., Rivera, R., Hooper, M.H., Catravas, J., 2017. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. Chest 151, 1229-1238.

Markwart, R., Condotta, S.A., Requardt, R.P., Borken, F., Schubert, K., Weigel, C., Bauer, M., Griffith, T.S., Forster, M., Brunkhorst, F.M., Badovinac, V.P., Rubio, I., 2014. Immunosuppression after sepsis: systemic inflammation and sepsis induce a loss of naive T-cells but no enduring cell-autonomous defects in T-cell function. PloS one 9, e115094.

Marshall, J.C., 2004. Sepsis: current status, future prospects. Current opinion in critical care 10, 250-264.

Martignoni, A., Tschop, J., Goetzman, H.S., Choi, L.G., Reid, M.D., Johannigman, J.A., Lentsch, A.B., Caldwell, C.C., 2008. CD4-expressing cells are early mediators of the innate immune system during sepsis. Shock (Augusta, Ga.) 29, 591-597.

Martinez-Lostao, L., Anel, A., Pardo, J., 2015. How Do Cytotoxic Lymphocytes Kill Cancer Cells? Clinical cancer research : an official journal of the American Association for Cancer Research 21, 5047-5056.

Mezrich, J.D., Fechner, J.H., Zhang, X., Johnson, B.P., Burlingham, W.J., Bradfield, C.A., 2010. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. Journal of immunology (Baltimore, Md. : 1950) 185, 3190-3198.

Michalek, R.D., Gerriets, V.A., Jacobs, S.R., Macintyre, A.N., MacIver, N.J., Mason, E.F., Sullivan, S.A., Nichols, A.G., Rathmell, J.C., 2011. Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4+ T cell subsets. Journal of immunology (Baltimore, Md. : 1950) 186, 3299-3303.

Mills, K.H., McGuirk, P., 2004. Antigen-specific regulatory T cells--their induction and role in infection. Seminars in immunology 16, 107-117.

Mocanu, V., Oboroceanu, T., Zugun-Eloae, F., 2013. Current status in vitamin D and regulatory T cells--immunological implications. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi 117, 965-973.

Monneret, G., Debard, A.-L., Venet, F., Bohe, J., Hequet, O., Bienvenu, J., Lepape, A., 2003. Marked elevation of human circulating CD4+CD25+ regulatory T cells in sepsis-induced immunoparalysis. Critical care medicine 31, 2068-2071.

Monserrat, J., de Pablo, R., Diaz-Martín, D., Rodríguez-Zapata, M., de la Hera, A., Prieto, A., Alvarez-Mon, M., 2013. Early alterations of B cells in patients with septic shock. Critical Care 17, R105-R105.

Moromizato, T., Litonjua, A.A., Braun, A.B., Gibbons, F.K., Giovannucci, E., Christopher, K.B., 2014. Association of low serum 25-hydroxyvitamin D levels and sepsis in the critically ill. Critical care medicine 42, 97-107.

Nakaya, M., Xiao, Y., Zhou, X., Chang, J.H., Chang, M., Cheng, X., Blonska, M., Lin, X., Sun, S.C., 2014. Inflammatory T cell responses rely on amino acid transporter ASCT2 facilitation of glutamine uptake and mTORC1 kinase activation. Immunity 40, 692-705.

Nascimento, D.C., Melo, P.H., Piñeros, A.R., Ferreira, R.G., Colón, D.F., Donate, P.B., Castanheira, F.V., Gozzi, A., Czaikoski, P.G., Niedbala, W., Borges, M.C., Zamboni, D.S., Liew, F.Y., Cunha, F.Q., Alves-

Filho, J.C., 2017. IL-33 contributes to sepsis-induced long-term immunosuppression by expanding the regulatory T cell population. Nature Communications 8, 14919.
Newton, R., Priyadharshini, B., Turka, L.A., 2016. Immunometabolism of regulatory T cells. Nature immunology 17, 618-625.
Nie, Z., Hu, G., Wei, G., Cui, K., Yamane, A., Resch, W., Wang, R., Green, D.R., Tessarollo, L., Casellas, R., Zhao, K., Levens, D., 2012. c-Myc is a universal amplifier of expressed genes in lymphocytes and embryonic stem cells. Cell 151, 68-79.
O'Brien, T.F., Gorentla, B.K., Xie, D., Srivatsan, S., McLeod, I.X., He, Y.W., Zhong, X.P., 2011. Regulation of T-cell survival and mitochondrial homeostasis by TSC1. European journal of immunology 41, 3361-3370.
Oliveira, Y.P.A.d., Pontes-de-Carvalho, L.C., Couto, R.D., Noronha-Dutra, A.A., 2017. Oxidative stress in sepsis. Possible production of free radicals through an erythrocyte-mediated positive feedback mechanism. The Brazilian Journal of Infectious Diseases 21, 19-26.
Oren, R., Farnham, A.E., Saito, K., Milofsky, E., Karnovsky, M.L., 1963. Metabolic patterns in three types of phagocytizing cells. The Journal of cell biology 17, 487-501.
Otto, G.P., Sossdorf, M., Claus, R.A., Rodel, J., Menge, K., Reinhart, K., Bauer, M., Riedemann, N.C., 2011. The late phase of sepsis is characterized by an increased microbiological burden and death rate. Critical care (London, England) 15, R183.
Pachot, A., Monneret, G., Voirin, N., Leissner, P., Venet, F., Bohe, J., Payen, D., Bienvenu, J., Mougin, B., Lepape, A., 2005. Longitudinal study of cytokine and immune transcription factor mRNA expression in septic shock. Clinical immunology (Orlando, Fla.) 114, 61-69.
Palazon, A., Goldrath, A.W., Nizet, V., Johnson, R.S., 2014. HIF transcription factors, inflammation, and immunity. Immunity 41, 518-528.
Pandiyan, P., Zheng, L., Lenardo, M.J., 2011. The Molecular Mechanisms of Regulatory T Cell Immunosuppression. Frontiers in immunology 2, 60.
Panieri, E., Santoro, M.M., 2016. ROS homeostasis and metabolism: a dangerous liason in cancer cells. Cell death & disease 7, e2253.
Parekh, D., Patel, J.M., Scott, A., Lax, S., Dancer, R.C.A., D'Souza, V., Greenwood, H., Fraser, W.D., Gao, F., Sapey, E., Perkins, G.D., Thickett, D.R., 2017. Vitamin D Deficiency in Human and Murine Sepsis*. Critical care medicine 45, 282-289.
Park, B.V., Pan, F., 2015. Metabolic regulation of T cell differentiation and function. Molecular immunology 68, 497-506.
Park, Y., Jin, H.S., Lopez, J., Elly, C., Kim, G., Murai, M., Kronenberg, M., Liu, Y.C., 2013. TSC1 regulates the balance between effector and regulatory T cells. The Journal of clinical investigation 123, 5165-5178.
Patel, C.H., Powell, J.D., 2017. Targeting T cell metabolism to regulate T cell activation, differentiation and function in disease. Current opinion in immunology 46, 82-88.
Patil, N.K., Bohannon, J.K., Sherwood, E.R., 2016. Immunotherapy: A promising approach to reverse sepsis-induced immunosuppression. Pharmacological research 111, 688-702.
Pearce, E.L., Walsh, M.C., Cejas, P.J., Harms, G.M., Shen, H., Wang, L.S., Jones, R.G., Choi, Y., 2009. Enhancing CD8 T-cell memory by modulating fatty acid metabolism. Nature 460, 103-107.
Peck, A., Mellins, E.D., 2010. Precarious balance: Th17 cells in host defense. Infection and immunity 78, 32-38.
Peyssonnaux, C., Cejudo-Martin, P., Doedens, A., Zinkernagel, A.S., Johnson, R.S., Nizet, V., 2007. Cutting edge: Essential role of hypoxia inducible factor-1alpha in development of lipopolysaccharide-induced sepsis. Journal of immunology (Baltimore, Md. : 1950) 178, 7516-7519.
Phetsouphanh, C., Pillai, S., Zaunders, J.J., 2017. Editorial: Cytotoxic CD4+ T Cells in Viral Infections. Frontiers in immunology 8.
Piccirillo, C.A., Shevach, E.M., 2004. Naturally-occurring CD4+CD25+ immunoregulatory T cells: central players in the arena of peripheral tolerance. Seminars in immunology 16, 81-88.

Poffenberger, M.C., Jones, R.G., 2014. Amino acids fuel T cell-mediated inflammation. Immunity 40, 635-637.
Pollizzi, K.N., Patel, C.H., Sun, I.H., Oh, M.H., Waickman, A.T., Wen, J., Delgoffe, G.M., Powell, J.D., 2015. mTORC1 and mTORC2 selectively regulate CD8(+) T cell differentiation. The Journal of clinical investigation 125, 2090-2108.
Previte, D.M., O'Connor, E.C., Novak, E.A., Martins, C.P., Mollen, K.P., Piganelli, J.D., 2017. Reactive oxygen species are required for driving efficient and sustained aerobic glycolysis during CD4+ T cell activation. PloS one 12, e0175549.
Previte, D.M., Piganelli, J.D., 2017. Reactive Oxygen Species and Their Implications on CD4(+) T Cells in Type 1 Diabetes. Antioxidants & redox signaling.
Prietl, B., Pilz, S., Wolf, M., Tomaschitz, A., Obermayer-Pietsch, B., Graninger, W., Pieber, T.R., 2010. Vitamin D supplementation and regulatory T cells in apparently healthy subjects: vitamin D treatment for autoimmune diseases? The Israel Medical Association journal : IMAJ 12, 136-139.
Procaccini, C., Carbone, F., Di Silvestre, D., Brambilla, F., De Rosa, V., Galgani, M., Faicchia, D., Marone, G., Tramontano, D., Corona, M., Alviggi, C., Porcellini, A., La Cava, A., Mauri, P., Matarese, G., 2016. The Proteomic Landscape of Human Ex Vivo Regulatory and Conventional T Cells Reveals Specific Metabolic Requirements. Immunity 44, 406-421.
Procaccini, C., De Rosa, V., Galgani, M., Abanni, L., Cali, G., Porcellini, A., Carbone, F., Fontana, S., Horvath, T.L., La Cava, A., Matarese, G., 2010. An oscillatory switch in mTOR kinase activity sets regulatory T cell responsiveness. Immunity 33, 929-941.
Procaccini, C., La Rocca, C., Carbone, F., De Rosa, V., Galgani, M., Matarese, G., 2017. Leptin as immune mediator: Interaction between neuroendocrine and immune system. Developmental and comparative immunology 66, 120-129.
Procaccini, C., Pucino, V., Mantzoros, C.S., Matarese, G., 2015. Leptin in autoimmune diseases. Metabolism: clinical and experimental 64, 92-104.
Quraishi, S.A., De Pascale, G., Needleman, J.S., Nakazawa, H., Kaneki, M., Bajwa, E.K., Camargo, C.A., Jr., Bhan, I., 2015. Effect of Cholecalciferol Supplementation on Vitamin D Status and Cathelicidin Levels in Sepsis: A Randomized, Placebo-Controlled Trial. Critical care medicine 43, 1928-1937.
Rabb, H., 2002. The T cell as a bridge between innate and adaptive immune systems: Implications for the kidney. Kidney International 61, 1935-1946.
Ranieri , V.M., Thompson , B.T., Barie , P.S., Dhainaut , J.-F., Douglas , I.S., Finfer , S., Gårdlund , B., Marshall , J.C., Rhodes , A., Artigas , A., Payen , D., Tenhunen , J., Al-Khalidi , H.R., Thompson , V., Janes , J., Macias , W.L., Vangerow , B., Williams , M.D., 2012. Drotrecogin Alfa (Activated) in Adults with Septic Shock. New England Journal of Medicine 366, 2055-2064.
Rao, E., Zhang, Y., Zhu, G., Hao, J., Persson, X.M., Egilmez, N.K., Suttles, J., Li, B., 2015. Deficiency of AMPK in CD8+ T cells suppresses their anti-tumor function by inducing protein phosphatase-mediated cell death. Oncotarget 6, 7944-7958.
Rathmell, J.C., Vander Heiden, M.G., Harris, M.H., Frauwirth, K.A., Thompson, C.B., 2000. In the absence of extrinsic signals, nutrient utilization by lymphocytes is insufficient to maintain either cell size or viability. Molecular cell 6, 683-692.
Rendon, J.L., Choudhry, M.A., 2012. Th17 cells: critical mediators of host responses to burn injury and sepsis. Journal of leukocyte biology 92, 529-538.
Rimmele, T., Payen, D., Cantaluppi, V., Marshall, J., Gomez, H., Gomez, A., Murray, P., Kellum, J.A., 2016. IMMUNE CELL PHENOTYPE AND FUNCTION IN SEPSIS. Shock (Augusta, Ga.) 45, 282-291.
Roberts, D.J., Miyamoto, S., 2015. Hexokinase II integrates energy metabolism and cellular protection: Akting on mitochondria and TORCing to autophagy. Cell Death and Differentiation 22, 248-257.
Roberts, D.J., Tan-Sah, V.P., Smith, J.M., Miyamoto, S., 2013. Akt phosphorylates HK-II at Thr473 and increases mitochondrial HK-II association to protect cardiomyocytes. Journal of Biological Chemistry.
Rocha, M., Herance, R., Rovira, S., Hernandez-Mijares, A., Victor, V.M., 2012. Mitochondrial dysfunction and antioxidant therapy in sepsis. Infectious disorders drug targets 12, 161-178.

Rolf, J., Zarrouk, M., Finlay, D.K., Foretz, M., Viollet, B., Cantrell, D.A., 2013. AMPKalpha1: a glucose sensor that controls CD8 T-cell memory. European journal of immunology 43, 889-896.
Romagnani, S., Maggi, E., Liotta, F., Cosmi, L., Annunziato, F., 2009. Properties and origin of human Th17 cells. Molecular immunology 47, 3-7.
Rossi, F., Romeo, D., Patriarca, P., 1972. Mechanism of phagocytosis-associated oxidative metabolism in polymorphonuclear leucocytes and macrophages. Journal of the Reticuloendothelial Society 12, 127-149.
Rossi, F., Zatti, M., 1964. CHANGES IN THE METABOLIC PATTERN OF POLYMORPHO-NUCLEAR LEUCOCYTES DURING PHAGOCYTOSIS. British journal of experimental pathology 45, 548-559.
Sage, P.T., Ron-Harel, N., Juneja, V.R., Sen, D.R., Maleri, S., Sungnak, W., Kuchroo, V.K., Haining, W.N., Chevrier, N., Haigis, M., Sharpe, A.H., 2016. Suppression by TFR cells leads to durable and selective inhibition of B cell effector function. Nature immunology 17, 1436.
Sasaki, C.Y., Chen, G., Munk, R., Eitan, E., Martindale, J., Longo, D.L., Ghosh, P., 2016. p((7)(0)S(6)K(1)) in the TORC1 pathway is essential for the differentiation of Th17 Cells, but not Th1, Th2, or Treg cells in mice. European journal of immunology 46, 212-222.
Saxton, R.A., Knockenhauer, K.E., Wolfson, R.L., Chantranupong, L., Pacold, M.E., Wang, T., Schwartz, T.U., Sabatini, D.M., 2016. Structural basis for leucine sensing by the Sestrin2-mTORC1 pathway. Science (New York, N.Y.) 351, 53-58.
Scharping, N.E., Menk, A.V., Moreci, R.S., Whetstone, R.D., Dadey, R.E., Watkins, S.C., Ferris, R.L., Delgoffe, G.M., 2016. The Tumor Microenvironment Represses T Cell Mitochondrial Biogenesis to Drive Intratumoral T Cell Metabolic Insufficiency and Dysfunction. Immunity 45, 374-388.
Schmidt, A., Oberle, N., Krammer, P.H., 2012. Molecular mechanisms of treg-mediated T cell suppression. Frontiers in immunology 3, 51.
Schmoeckel, K., Traffehn, S., Eger, C., Pötschke, C., Bröker, B.M., 2015. Full Activation of CD4+ T Cells Early During Sepsis Requires Specific Antigen. Shock (Augusta, Ga.) 43, 192-200.
Scumpia, P.O., Delano, M.J., Kelly, K.M., O'Malley, K.A., Efron, P.A., McAuliffe, P.F., Brusko, T., Ungaro, R., Barker, T., Wynn, J.L., Atkinson, M.A., Reeves, W.H., Clare Salzler, M.J., Moldawer, L.L., 2006. Increased Natural $CD4^{+}CD25^{+}$ Regulatory T Cells and Their Suppressor Activity Do Not Contribute to Mortality in Murine Polymicrobial Sepsis. The Journal of Immunology 177, 7943-7949.
Sehrawat, S., Rouse, B.T., 2017. Interplay of Regulatory T Cell and Th17 Cells during Infectious Diseases in Humans and Animals. Frontiers in immunology 8.
Shapiro, N.I., Khankin, E.V., Van Meurs, M., Shih, S.-C., Lu, S., Yano, M., Castro, P.R., Maratos-Flier, E., Parikh, S.M., Karumanchi, S.A., Yano, K., 2010. Leptin Exacerbates Sepsis-Mediated Morbidity and Mortality. Journal of immunology (Baltimore, Md. : 1950) 185, 517-524.
Shelley, O., Murphy, T., Paterson, H., Mannick, J.A., Lederer, J.A., 2003. Interaction between the innate and adaptive immune systems is required to survive sepsis and control inflammation after injury. Shock (Augusta, Ga.) 20, 123-129.
Shi, L.Z., Wang, R., Huang, G., Vogel, P., Neale, G., Green, D.R., Chi, H., 2011. HIF1alpha-dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of TH17 and Treg cells. The Journal of experimental medicine 208, 1367-1376.
Shindo, Y., Fuchs, A.G., Davis, C.G., Eitas, T., Unsinger, J., Burnham, C.D., Green, J.M., Morre, M., Bochicchio, G.V., Hotchkiss, R.S., 2017. Interleukin 7 immunotherapy improves host immunity and survival in a two-hit model of Pseudomonas aeruginosa pneumonia. Journal of leukocyte biology 101, 543-554.
Shinkai, K., Mohrs, M., Locksley, R.M., 2002. Helper T cells regulate type-2 innate immunity in vivo. Nature 420, 825-829.
Sinclair, L.V., Rolf, J., Emslie, E., Shi, Y.B., Taylor, P.M., Cantrell, D.A., 2013. Control of amino-acid transport by antigen receptors coordinates the metabolic reprogramming essential for T cell differentiation. Nature immunology 14, 500-508.
Singer, M., Deutschman, C.S., Seymour, C.W., Shankar-Hari, M., Annane, D., Bauer, M., Bellomo, R., Bernard, G.R., Chiche, J.-D., Coopersmith, C.M., Hotchkiss, R.S., Levy, M.M., Marshall, J.C., Martin, G.S.,

Opal, S.M., Rubenfeld, G.D., van der Poll, T., Vincent, J.-L., Angus, D.C., 2016. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Jama 315, 801-810.
Smyk-Pearson, S.K., Bakke, A.C., Held, P.K., Wildin, R.S., 2003. Rescue of the autoimmune scurfy mouse by partial bone marrow transplantation or by injection with T-enriched splenocytes. Clinical and Experimental Immunology 133, 193-199.
Standage, S.W., Caldwell, C.C., Zingarelli, B., Wong, H.R., 2012. Reduced peroxisome proliferator-activated receptor alpha expression is associated with decreased survival and increased tissue bacterial load in sepsis. Shock (Augusta, Ga.) 37, 164-169.
Sun, L., Fu, J., Zhou, Y., 2017. Metabolism Controls the Balance of Th17/T-Regulatory Cells. Frontiers in immunology 8.
Tatura, R., Zeschnigk, M., Hansen, W., Steinmann, J., Goncalves Vidigal, P., Hutzler, M., Pastille, E., Westendorf, A.M., Buer, J., Kehrmann, J., 2015. Relevance of Foxp3(+) regulatory T cells for early and late phases of murine sepsis. Immunology 146, 144-156.
Terrazzano, G., Rubino, V., Damiano, S., Sasso, A., Petrozziello, T., Ucci, V., Palatucci, A.T., Giovazzino, A., Santillo, M., De Felice, B., Garbi, C., Mondola, P., Ruggiero, G., 2014. T cell activation induces CuZn superoxide dismutase (SOD)-1 intracellular re-localization, production and secretion. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research 1843, 265-274.
Textoris, J., Beaufils, N., Quintana, G., Ben Lassoued, A., Zieleskiewicz, L., Wiramus, S., Blasco, V., Lesavre, N., Martin, C., Gabert, J., Leone, M., 2012. Hypoxia-inducible factor (HIF1α) gene expression in human shock states. Critical Care 16, R120.
Tzanela, M., Orfanos, S.E., Tsirantonaki, M., Kotanidou, A., Sotiropoulou, C., Christophoraki, M., Vassiliadi, D., Thalassinos, N.C., Roussos, C., 2006. Leptin alterations in the course of sepsis in humans. In vivo (Athens, Greece) 20, 565-570.
Unsinger, J., Herndon, J.M., Davis, C.G., Muenzer, J.T., Hotchkiss, R.S., Ferguson, T.A., 2006. The role of TCR engagement and activation-induced cell death in sepsis-induced T cell apoptosis. Journal of immunology (Baltimore, Md. : 1950) 177, 7968-7973.
Upala, S., Sanguankeo, A., Permpalung, N., 2015. Significant association between vitamin D deficiency and sepsis: a systematic review and meta-analysis. BMC Anesthesiology 15, 84.
van de Veerdonk, F.L., Mouktaroudi, M., Ramakers, B.P., Pistiki, A., Pickkers, P., van der Meer, J.W., Netea, M.G., Giamarellos-Bourboulis, E.J., 2012. Deficient Candida-specific T-helper 17 response during sepsis. The Journal of infectious diseases 206, 1798-1802.
Van den Bossche, J., O'Neill, L.A., Menon, D., 2017. Macrophage Immunometabolism: Where Are We (Going)? Trends in immunology 38, 395-406.
van der Veeken, J., Gonzalez, A.J., Cho, H., Arvey, A., Hemmers, S., Leslie, C.S., Rudensky, A.Y., 2016. Memory of Inflammation in Regulatory T Cells. Cell 166, 977-990.
Venet, F., Chung, C.S., Kherouf, H., Geeraert, A., Malcus, C., Poitevin, F., Bohe, J., Lepape, A., Ayala, A., Monneret, G., 2009. Increased circulating regulatory T cells (CD4(+)CD25 (+)CD127 (-)) contribute to lymphocyte anergy in septic shock patients. Intensive care medicine 35, 678-686.
Venet, F., Demaret, J., Blaise, B.J., Rouget, C., Girardot, T., Idealisoa, E., Rimmele, T., Mallet, F., Lepape, A., Textoris, J., Monneret, G., 2017. IL-7 Restores T Lymphocyte Immunometabolic Failure in Septic Shock Patients through mTOR Activation. Journal of immunology (Baltimore, Md. : 1950) 199, 1606-1615.
Venet, F., Monneret, G., 2017. Advances in the understanding and treatment of sepsis-induced immunosuppression. Nature reviews. Nephrology.
Venet, F., Pachot, A., Debard, A.L., Bohe, J., Bienvenu, J., Lepape, A., Monneret, G., 2004. Increased percentage of CD4+CD25+ regulatory T cells during septic shock is due to the decrease of CD4+CD25- lymphocytes. Critical care medicine 32, 2329-2331.
Venet, F., Rimmele, T., Monneret, G., 2018. Management of Sepsis-Induced Immunosuppression. Critical care clinics 34, 97-106.
Villa, P., Saccani, A., Sica, A., Ghezzi, P., 2002. Glutathione Protects Mice from Lethal Sepsis by Limiting Inflammation and Potentiating Host Defense. The Journal of infectious diseases 185, 1115-1120.

von Knethen, A., Soller, M., Brüne, B., 2007. Peroxisome proliferator-activated receptor γ (PPARγ) and sepsis. Archivum Immunologiae et Therapiae Experimentalis 55, 19-25.
Waickman, A.T., Powell, J.D., 2012. mTOR, metabolism, and the regulation of T-cell differentiation and function. Immunological reviews 249, 43-58.
Wang, R., Dillon, C.P., Shi, L.Z., Milasta, S., Carter, R., Finkelstein, D., McCormick, L.L., Fitzgerald, P., Chi, H., Munger, J., Green, D.R., 2011. The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. Immunity 35, 871-882.
Wang, R., Solt, L.A., 2016. Metabolism of murine TH 17 cells: Impact on cell fate and function. European journal of immunology 46, 807-816.
Wang, S.D., Huang, K.J., Lin, Y.S., Lei, H.Y., 1994. Sepsis-induced apoptosis of the thymocytes in mice. Journal of immunology (Baltimore, Md. : 1950) 152, 5014-5021.
Ward, P.A., 2012. New approaches to the study of sepsis. EMBO molecular medicine 4, 1234-1243.
Wawman, R.E., Bartlett, H., Oo, Y.H., 2017. Regulatory T Cell Metabolism in the Hepatic Microenvironment. Frontiers in immunology 8, 1889.
Weber, G.F., Swirski, F.K., 2014. Immunopathogenesis of abdominal sepsis. Langenbeck's archives of surgery 399, 1-9.
Wei, J., Long, L., Yang, K., Guy, C., Shrestha, S., Chen, Z., Wu, C., Vogel, P., Neale, G., Green, D.R., Chi, H., 2016. Autophagy enforces functional integrity of regulatory T cells by coupling environmental cues and metabolic homeostasis. Nature immunology 17, 277-285.
Werth, N., Beerlage, C., Rosenberger, C., Yazdi, A.S., Edelmann, M., Amr, A., Bernhardt, W., von Eiff, C., Becker, K., Schäfer, A., Peschel, A., Kempf, V.A.J., 2010. Activation of Hypoxia Inducible Factor 1 Is a General Phenomenon in Infections with Human Pathogens. PloS one 5, e11576.
Weyand, C.M., Goronzy, J.J., 2017. Immunometabolism in early and late stages of rheumatoid arthritis. Nature reviews. Rheumatology 13, 291-301.
Weyand, C.M., Zeisbrich, M., Goronzy, J.J., 2017. Metabolic signatures of T-cells and macrophages in rheumatoid arthritis. Current opinion in immunology 46, 112-120.
Wofford, J.A., Wieman, H.L., Jacobs, S.R., Zhao, Y., Rathmell, J.C., 2008. IL-7 promotes Glut1 trafficking and glucose uptake via STAT5-mediated activation of Akt to support T-cell survival. Blood 111, 2101-2111.
Wolfson, R.L., Chantranupong, L., Saxton, R.A., Shen, K., Scaria, S.M., Cantor, J.R., Sabatini, D.M., 2016. Sestrin2 is a leucine sensor for the mTORC1 pathway. Science (New York, N.Y.) 351, 43-48.
Wu, H.P., Chung, K., Lin, C.Y., Jiang, B.Y., Chuang, D.Y., Liu, Y.C., 2013. Associations of T helper 1, 2, 17 and regulatory T lymphocytes with mortality in severe sepsis. Inflammation research : official journal of the European Histamine Research Society ... [et al.] 62, 751-763.
Wu, Q., Liu, Y., Chen, C., Ikenoue, T., Qiao, Y., Li, C.S., Li, W., Guan, K.L., Liu, Y., Zheng, P., 2011. The tuberous sclerosis complex-mammalian target of rapamycin pathway maintains the quiescence and survival of naive T cells. Journal of immunology (Baltimore, Md. : 1950) 187, 1106-1112.
Xu, F.Y., Taylor, W.A., Hurd, J.A., Hatch, G.M., 2003. Etomoxir mediates differential metabolic channeling of fatty acid and glycerol precursors into cardiolipin in H9c2 cells. Journal of lipid research 44, 415-423.
Xu, T., Stewart, K.M., Wang, X., Liu, K., Xie, M., Kyu Ryu, J., Li, K., Ma, T., Wang, H., Ni, L., Zhu, S., Cao, N., Zhu, D., Zhang, Y., Akassoglou, K., Dong, C., Driggers, E.M., Ding, S., 2017. Metabolic control of TH17 and induced Treg cell balance by an epigenetic mechanism. Nature 548, 228-233.
Yan, Z., Xiaoyu, Z., Zhixin, S., Di, Q., Xinyu, D., Jing, X., Jing, H., Wang, D., Xi, Z., Chunrong, Z., Daoxin, W., 2016. Rapamycin attenuates acute lung injury induced by LPS through inhibition of Th17 cell proliferation in mice. Scientific Reports 6, 20156.
Yang, J., Sundrud, M.S., Skepner, J., Yamagata, T., 2014. Targeting Th17 cells in autoimmune diseases. Trends Pharmacol Sci 35, 493-500.
Yang, K., Chi, H., 2012. mTOR and metabolic pathways in T cell quiescence and functional activation. Seminars in immunology 24, 421-428.

Yang, Z., Matteson, E.L., Goronzy, J.J., Weyand, C.M., 2015. T-cell metabolism in autoimmune disease. Arthritis research & therapy 17, 29.
Ye, J., Livergood, R.S., Peng, G., 2013. The Role and Regulation of Human Th17 Cells in Tumor Immunity. The American Journal of Pathology 182, 10-20.
Yen, Y.T., Yang, H.R., Lo, H.C., Hsieh, Y.C., Tsai, S.C., Hong, C.W., Hsieh, C.H., 2013. Enhancing autophagy with activated protein C and rapamycin protects against sepsis-induced acute lung injury. Surgery 153, 689-698.
Yousef, A.A.A.-M., Amr, Y.M., Suliman, G.A., 2010. The diagnostic value of serum leptin monitoring and its correlation with tumor necrosis factor-α in critically ill patients: a prospective observational study. Critical Care 14, R33.
Yu, Z.-x., Ji, M.-s., Yan, J., Cai, Y., Liu, J., Yang, H.-f., Li, Y., Jin, Z.-c., Zheng, J.-x., 2015a. The ratio of Th17/Treg cells as a risk indicator in early acute respiratory distress syndrome. Critical Care 19, 82.
Yu, Z.X., Ji, M.S., Yan, J., Cai, Y., Liu, J., Yang, H.F., Li, Y., Jin, Z.C., Zheng, J.X., 2015b. The ratio of Th17/Treg cells as a risk indicator in early acute respiratory distress syndrome. Critical care (London, England) 19, 82.
Zeng, H., Chi, H., 2015. Metabolic control of regulatory T cell development and function. Trends in immunology 36, 3-12.
Zeng, H., Yang, K., Cloer, C., Neale, G., Vogel, P., Chi, H., 2013. mTORC1 couples immune signals and metabolic programming to establish T(reg)-cell function. Nature 499, 485-490.
Zhang, L., Romero, P., 2018. Metabolic Control of CD8(+) T Cell Fate Decisions and Antitumor Immunity. Trends in molecular medicine 24, 30-48.
Zhang, M., Dong, Y., Hu, F., Yang, D., Zhao, Q., Lv, C., Wang, Y., Xia, C., Weng, Q., Liu, X., Li, C., Zhou, P., Wang, T., Guan, Y., Guo, R., Liu, L., Geng, Y., Wu, H., Du, J., Hu, Z., Xu, S., Chen, J., He, A., Liu, B., Wang, D., Yang, Y.-G., Wang, J., 2018. Transcription factor Hoxb5 reprograms B cells into functional T lymphocytes. Nature immunology.
Zingarelli, B., Cook, J.A., 2005. Peroxisome proliferator-activated receptor-gamma is a new therapeutic target in sepsis and inflammation. Shock (Augusta, Ga.) 23, 393-399.
Zingarelli, B., Piraino, G., Hake, P.W., O'Connor, M., Denenberg, A., Fan, H., Cook, J.A., 2010. Peroxisome proliferator-activated receptor {delta} regulates inflammation via NF-{kappa}B signaling in polymicrobial sepsis. Am J Pathol 177, 1834-1847.

Figure Captions

Figure 1. Immunometabolic pathways and their regulation in quiescent conventional T cells. The activation of CD28 and TCR controls metabolic reprogramming of T cells via AMPK, and Akt pathway. For example, activation of AMPK negatively impacts lipid synthesis and mTOR signaling. While it activates FAO. For proper functioning of T cells under normal conditions OXPHOS is required that is controlled by aerobic glycolysis, glutaminolysis, and FAO. The interaction of IL-7 with IL-7R via activation of STA5 controls glucose uptake and glycolysis. Details are mentioned in text.

Figure 2. Regulatory T cell (Tregs) metabolism during normal and inflammatory conditions. Tregs have higher number of mitochondria as compared to other types of T cells. Both glycolysis and FAO are required for effective effective OXPHOS in both Tregs and iTregs. However, IL-2R and TCR mediated activation of mTORC1 is responsible for lipid and cholesterol synthesis that plays role in an increased FAO and OXPHOS required for Tregs immunosuppressive function. Induction of HIF-1α in Tregs proves detrimental to them as it degrades Foxp3, thus impairs their differentiation. However, during inflammatory conditions/environment, Foxp3 suppresses c-Myc expression and thus the glycolysis to further promote OXPHOS. Tregs are able to maintain their redox balance under low glucose/high-lactate concentration due to the generation of NAD^+ via TCA cycle. Thus, in low glucose/high-lactate conditions, increased survival of Tregs causes an increased state of immunosuppression as observed in later immunosuppressive stage of sepsis. See text for detail.

Fig 1

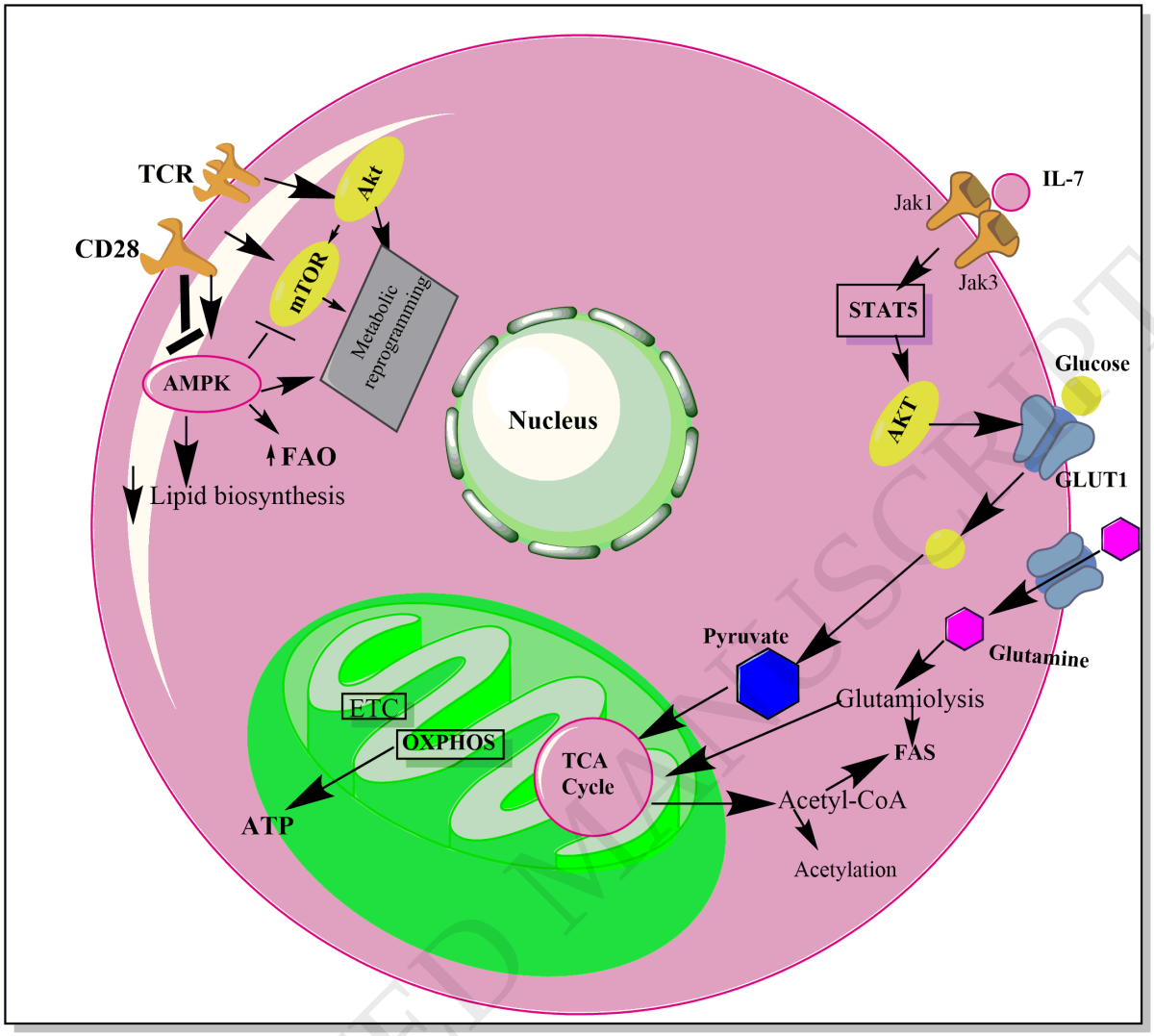


Fig 2