The Interconnection Between Immuno-Metabolism, Diabetes, and CKD

Fabrizia Bonacina [1] · Andrea Baragetti [1,2] · Alberico Luigi Catapano [1,3] · Giuseppe Danilo Norata [1,2]

Abstract

Purpose of Review Metabolic reprogramming is increasingly recognized as an essential trait of functional activation of immune cells. Here, we describe the link between immuno-metabolism, diabetes, and diabetic nephropathy.

Recent Findings Crosstalk between cellular metabolic functions and immune activation occurs when plasma levels of glucose, triglycerides, and free fatty acids increase, thus promoting systemic low-grade inflammation that further boosts the development of metabolic complications. In the long run, this settles an "apparent paradox," where, despite excessive inflammation, the immune system is suppressed, further promoting progression to end-stage renal disease (ESRD) and predisposing to premature deaths from infections and cardiovascular diseases. Reviewing the effects of diabetes treatments on immuno-inflammatory responses suggests that the benefit of these drugs might extend beyond the simple control of glucose homeostasis.

Summary Hyperglycemia and dyslipidemia correlate with enhancement of the immuno-inflammatory response that can promote and worsen metabolic diseases and support the progression toward ESRD. The identification of cellular checkpoints that modulate the immuno-metabolic machinery of immune cells opens new venues for metabolic drugs.

Keywords Immune response · Metabolism · Diabetes · Kidney disease

Introduction—Immuno-Metabolism

Immuno-metabolism represents a novel field of research that specifically investigates how dynamic changes in

Fabrizia Bonacina and Andrea Baragetti contributed equally to this work.

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✉ Giuseppe Danilo Norata
danilo.norata@unimi.it

Fabrizia Bonacina
fabrizia.bonacina@unimi.it

Andrea Baragetti
andrea.baragetti@unimi.it

Alberico Luigi Catapano
alberico.catapano@unimi.it

[1] Department of Excellence of Pharmacological and Biomolecular Sciences (DisFeB), Università Degli Studi di Milano, Via Balzaretti 9, 20133 Milan, Italy

[2] SISA Centre, Bassini Hospital, 20092 Cinisello Balsamo, Italy

[3] IRCSS Multimedica, 20138 Milan, Italy

the metabolic machinery of the immune cells affect their activation, proliferation, mobilization, and acquisition of effector or regulatory functions [1••]. Indeed, immune cell activation and proliferation are coupled to anabolic pathways that provide the energy necessary for the production of macromolecules. Quiescent, non-proliferating cells, in contrast, require nutrient catabolism to sustain cell maintenance. Therefore, the balance between anaerobic glycolysis and mitochondrial tricarboxylic acid (TCA) cycle coupled to oxidative phosphorylation (OXPHOS) is likely to influence the functional fate of the immune cells. In addition to this, nutrient availability may shape immune functions by influencing the intracellular metabolism, thus suggesting a mechanism for a direct effect on the immune response. This appears to be the case in obesity where the combination of dyslipidemia and hyperglycemia triggers a state of chronic, low-grade inflammation, leading to the development of insulin resistance, and eventually diabetes [2]. Whether systemic metabolic derangement precedes or follows the dysregulation of the immuno-inflammatory response remains controversial (Fig. 1). The aim of this review is to discuss recent findings on how metabolic repro-

Fig. 1 Immuno-metabolic adaptations during diabetes. Development of obesity, insulin resistance, and β-cell dysfunction are closely associated with failure of systemic metabolism. Loss of metabolic homeostasis is usually the consequence of several risk factors with hyperglycemia and dyslipidemia being the most important. These alterations lead to metabolic adaptations at cellular levels also in immune cells which adapt their setting from a anti-inflammatory/ tolerogenic to a pro-inflammatory/activated status. The immuno-metabolic rewiring may in turn support systemic metabolic dysfunction, thus leading to the exacerbation of diabetes and its complications. Targeting metabolic pathways in immune cells may therefore promise a novel therapeutic approach to limit metabolic-driven immuno-inflammatory response that associates with diabetes and its complications. Indeed, limiting downstream signaling of immuno-metabolic checkpoints, as TLR4 and CD36, may impact the pro-inflammatory response, while the metabolic rewiring with the use of short-chain fatty acids (SCFA) or mannose might promote a tolerogenic, anti-inflammatory response, thus improving the immuno-inflammatory status and in concert, disease outcome
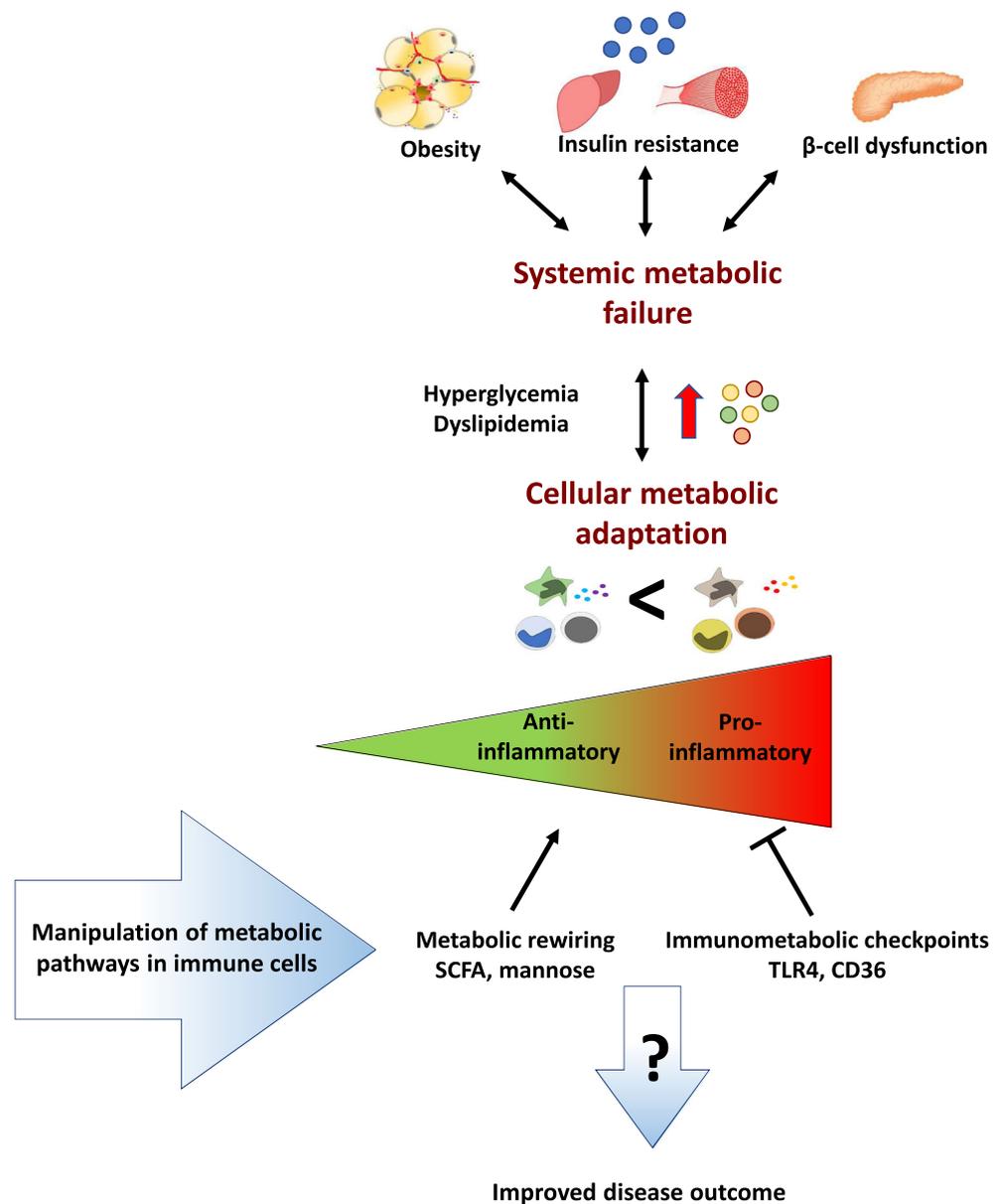
gramming in immune cells contributes to the development of diabetes and its complications such as kidney disease.

Crosstalk Between Systemic and Cellular Metabolic Alterations with Immuno-Inflammatory Responses in Diabetes

Excess calorie consumption predisposes to metabolic and inflammatory derangements that are associated with adverse clinical outcomes [3]. Ectopic fat accumulation, in particular in the abdominal cavity, prompts an inflammatory response which switches the pool of anti-inflammatory resident immune cells (those participating mainly in the resolution of the inflammatory response) toward an activated effector phenotype. These immune cells, in turn, sustain a systemic low-grade inflammatory response characterized by increased levels of pro-inflammatory cytokines [4]. This rise in systemic inflammation marks a transition toward pathological obesity and insulin resistance, culminating in diabetes and its complications, including chronic kidney disease [5]. Beyond the classically described picture of "a state of increased low-grade inflammation," changes occurring in circulating triglycerides, free fatty acids (FFA), and glucose directly impact the intracellular metabolism

of the immune cells and may promote changes in their energetic metabolism and, in concert, affect their activation status (Fig. 1).

Role of Lipids in the Immuno-Metabolic Rewiring of Immune Cells

The observation that FFAs are ligands of the toll-like receptors (TLR) 2 and TLR4 [6], and that TLR4 deficiency selectively protects mice from obesity induced by a diet enriched in saturated fats (HFD) [7], suggests that lipids play an immuno-modulatory role. For instance, palmitate, whose plasma levels increase during a high-fat diet, directly activates the inflammasome and promotes IL-1β and IL-18 secretion from macrophages. More recently, it has been shown that, parallel to the induction of the inflammatory response, prolonged TLR4 engagement triggers a feedback pathway, known as resolution phase that limits the excessive activation of macrophages. This biphasic response associated with TLR4 activation is driven initially by the activation of the canonical NF-κB pathway, followed later by de novo fatty acid biosynthesis, which is dependent on the activation of sterol regulatory element-binding protein 1 activity (SREBP1) that supports the anti-inflammatory response [8]. For instance, anti-inflammatory polyunsaturated FFAs, such as palmitoleate [9] and oleate [10], improve muscle insulin sensitivity in vitro and in animal models of metabolic diseases by reducing the macrophage inflammatory response [11, 12]. A similar anti-inflammatory effect associated with an improved metabolic phenotype was observed also in humans after palmitoleate administration [13]. TLR4 represents therefore a clear example of a cellular checkpoint that integrates metabolic and inflammatory signaling. Expanding the knowledge in this area might help define novel immuno-metabolic targets for therapeutic purposes.

On the other hand, the increased availability of lipids in obese mice provides a proliferative advantage to myeloid progenitors, which translates into an enhanced inflammatory response as a larger number of myeloid progenitors differentiate into macrophages and accumulate in the adipose tissue [14•]. This effect is observed even when these cells are transplanted into lean mice, but is prevented in mice that are genetically deficient in TLR4 or other components of its signaling cascade [15]. In addition, the alteration of lipid efflux as a consequence of deficiency of ATP-binding cassette transporters ABCA-1 and ABCG1 or apolipoprotein E leads to intracellular accumulation of lipids, mainly cholesterol, which has been shown to increase myelopoiesis [16], macrophage responsiveness [17, 18], and antigen-presenting function of the dendritic cells [19, 20], pointing also to a role for sterol metabolism in immune cell activation.

Similar cellular metabolic rewiring occurs in the cells of the adaptive immune system, such as lymphocytes. At the molecular level, nutrient-sensing pathways dictate the metabolic and functional fate of these immune cells. Increased anabolic requirements, e.g., those faced by proliferating activated T lymphocytes, trigger mTOR activation that in turn promotes upregulation of SREBP activity. The consequent increase in cholesterol and fatty acids (FA) influx boosts T cell proliferation by providing building blocks for proliferation and activation [21].

T lymphocytes resident in the adipose tissue switch to an activated phenotype because of increased fatty acid levels, which drive polarization toward an effector phenotype. T cells from obese patients show an increased activation and polarization to the effector memory phenotype compared with those of their lean counterparts [22•]. Moreover, upregulation of CD36 (a critical receptor involved in the uptake of FFAs as well as lipoproteins) by effector T cells might help provide the substrates needed for FFA oxidation (FAO) upon activation. On the other hand, in memory cells, long-living cells that can rapidly re-activate and proliferate upon re-exposure to the antigen FAO depends on FFA stored in cellular lipid droplets that are produced from glycolysis-driven de novo lipogenesis [23]. This evidence suggests an intimate connection between immune response and metabolic status, where cellular and systemic lipid handling dictates the activation of immune cells.

Effect of Hyperglycemia on Immune-Metabolic Interaction

In addition to lipid metabolism, glucose metabolism can also shape the effector functions of the immune cells by modifying their metabolic machinery. For instance, interferon gamma (IFN-γ) drives transient insulin resistance in muscles leading to a rise in plasma glucose and insulin levels which enhances glycolysis in CD8+ T cells, thus supporting their activation following viral infections. In the pre-diabetic state, this temporary hyperinsulinemia derails glucose homeostasis, thus contributing to glucose intolerance and diabetes [24•].

Engagement of this mechanism supports the significant integration between immune response and metabolic adaptation, thus suggesting that peripheral insulin resistance may represent a mechanism for assisting the immune system in fighting viral infections. Metabolic reprogramming also represents an adaptation to the local environment. For example, engagement of anaerobic glycolysis by adipose tissue macrophages may offer a survival advantage in the low oxygen tension within the adipose tissue [25]. In turn, promotion of anaerobic glycolysis and dampening of the TCA cycle couples with pro-inflammatory activation of macrophages toward M1 phenotype [26]. Although this immuno-metabolic adaptation represents a physiological response to metabolite

availability, in the long run, this chronic activation might turn into an uncontrolled, metabolically detrimental pro-inflammatory response promoting diabetes development.

Indeed, similar to what has been reported during dyslipidemia [27], hyperglycemia induces the proliferation and expansion of bone marrow myeloid progenitor cells and is associated with the increased number of circulating neutrophils and monocytes observed in diabetic mice [28].

Therefore, dietary composition and feeding status constitute two main factors contributing to immune activation via metabolic reprogramming in the hematopoietic compartment, as well as in the immune cells both in the circulation and in the periphery. In the setting of obesity and its metabolic complications, this activation is not always resolved and can contribute to a chronic inflammatory response promoting insulin resistance and diabetes.

Therapeutic Metabolic Reprogramming of Immune Cells

Thus, manipulation of metabolic pathways in immune cells may be a compelling strategy for immunotherapy in human diseases characterized by both immune and metabolic dysregulations. For example, a group of short-chain fatty acids (SCFA), such as acetate and butyrate, which are mainly derived from the microbiota metabolism, promote a tolerogenic response by B cells and T regulatory cells by epigenetic mechanisms. This protective mechanism delays the onset of diabetes by preserving pancreatic β-cells, whose failure is not only typical of type 1 diabetes but also frequently observed in patients with type 2 diabetes [29]. Enhancing the differentiation of CD4+ T cells toward T regulatory cells in vivo also represents an alternative strategy to control the immuno-inflammatory response in diabetes (Fig. 1). For instance, administration of mannose protects mice from autoimmune diabetes by boosting fatty acid oxidation that in turn promotes TGF-β activation, favoring CD4+ polarization toward a regulatory phenotype [30].

Limited findings are available on the possibility of reprogramming immune cell metabolism in diabetes. However, it is worth speculating that the quantity, as well as the type, of dietary nutrients, such as SCFA, can shape the immuno-metabolic responses and dictate the direction of immune activation (pathological versus tolerogenic). Identifying the link between cellular nutrient sensing pathways and immune activation may therefore offer new therapeutic targets to guide disease-specific modulation of immune responses.

Connections Between Immune Response in Diabetes and CKD Development

Among the multitude of complications in type 2 diabetes (T2DM), CKD represents one of the most life-threatening.

Obesity, hyperglycemia, and insulin resistance, coupled to CKD, set up an inflammatory vicious circle leading to aberrant immune responses and the onset of diabetic nephropathy complications [31••, 32]. The initial metabolic anomalies provide a boost to the inflammatory-immune response, which may exacerbate diabetes complications such as the impairment of renal function. However, in the long run, this state of chronic inflammation might result in overall depression of the immune system, manifesting with altered innate and adaptive immune functions [31••, 33, 34•]. This altered immune profile, together with the loss of muscle mass [35•], protein-energy wasting, and cardiovascular and bone disease, is believed to contribute to greater mortality in the population with chronic and end-stage kidney disease [31••].

Besides the clinical features, these pathophysiological consequences raise the need to better understand whether the relation between metabolism and inflammation in diabetes and renal disease is the consequence of cellular metabolic alterations or it precedes a metabolic reprogramming to enhance cellular resilience.

Metabolically Driven Cellular Inflammation Exacerbates Diabetes and Its Complications

The observed association between diabetes on the one hand and inflammation, oxidative stress and activation of the immune response on the other suggests that type 2 diabetes may be an inflammatory disease [36]. It is known that overfeeding and the resulting metabolic stress are associated with visceral adipose inflammation [37] and impairment of β-cell function [38], both of which contribute to the development of insulin resistance and to the escalation of systemic inflammation and metabolic complications [39]. However, it is unclear whether inflammation causes the systemic metabolic dysregulation, or if the activation of cellular anabolic pathways enhances the immune response by boosting immune cell expansion. T2DM progression can be supported by the activation of the immune response as a consequence of hyperglycemia and/or hyperlipidemia. The latter generates a pro-inflammatory milieu which causes increased monocyte recruitment to the pancreatic islets, as well as preferential differentiation of macrophages to the pro-inflammatory M1 phenotype [40]. Local recruitment of immune cells triggers islet cell immunity leading to B cell failure [41]. This, in turn, generates danger signals that further sustain the activation of both innate and adaptive immunity [42].

Furthermore, the observation that systemic CRP levels are already elevated in people with pre-diabetes, while whole blood cell count and levels of IL-1RA increase with the worsening of glycemic control [43], suggests that a vicious cycle between immuno-inflammation and metabolic alterations occurs which is likely to sustain peripheral insulin resistance and its ensuing complications.

These events may also predispose to renal injury. Indeed, increased circulating levels of pro-inflammatory cytokines, such as TNF-α, lead to the production of reactive oxygen species (ROS) that in turn induce renal endothelial cell dysfunction [44] and promote upregulation of the adhesion molecule ICAM-1 [45] and generation of advanced glycation end-products (AGE) that play an important pathogenic role in the pathogenesis of diabetic kidney disease [46].

Taken together, these data suggest that in diabetes, metabolic dysregulation leads to an exaggerated immuno-inflammatory response, which in turn exacerbates the progression of renal disease.

Inflammation and Cellular Metabolic Reprogramming in CKD

The development of diabetic kidney disease is characterized by several alterations in cellular, metabolic, and inflammatory markers which support the systemic nature of CKD [31••]. However, whether these associations indicate a causal link between immunity and renal damage is debated. Normal kidneys harbor different immune cells, such as dendritic cells (DCs), macrophages, and, to a lesser extent, lymphocytes [47]. These resident immune cells play a crucial role in the development of immune tolerance against circulating, innocuous low-molecular-weight proteins, such as food antigens and hormones [48]. These substances are filtered by the glomeruli and then re-absorbed and degraded by tubular epithelial cells and can be captured by renal DCs or reach the local lymph nodes via lymphatic drainage [49]. Therefore, increased flux of molecules, such as proteins and glucose (e.g., with excess nutrient consumption), as well as toxins, crystals, and intrinsic oxidative stress products, may act as intrinsic damage-associated molecular patterns (DAMPs) and drive sterile inflammation via activation of TLRs (TLR1 to TLR6) and inflammasome components in the renal DCs and macrophages [50, 51]. Increased glucose levels upregulate NADPH oxidase isoform 4 (Nox4), which is constitutively expressed in proximal tubular renal cells [52], increasing mitochondrial stress. NLRP3/inflammasome activation and cellular production of reactive oxygen species (ROS) are additional events supporting renal inflammatory and oxidative stress [52, 53]. This pathological burden can affect kidney and its functional units (the nephrons) at any level. In fact, complex mechanisms have been demonstrated linking renal electrolytes imbalance and oxidative stress, involving the activation of Na+/K+ ATPase/Src (proto-oncogene tyrosine-protein kinase)/Ras cascade at the renal tubular level, inducing ROS production and fibrosis. At the same time, the Na+/K+ ATPase/Src/Ras complex [54, 55] promotes NLRP3/inflammasome activation, interleukin-1beta secretion, and mesangial cell apoptosis, leading to hyperuricemia and proteinuria [56]. Metabolomic analyses of urine and serum from CKD patients revealed impairments in cellular anti-oxidant enzymes, TCA, and glycolytic intermediates as well as mitochondrial metabolites [57•, 58, 59]. These data support cellular energetic imbalance, usually associated with protein-energy wasting and cachexia, and mark a profound pro-inflammatory immuno-metabolic reprogramming. Moreover, with the onset of end-stage renal disease and exacerbation of comorbidities (for example hypertension), changes in nutritional supplies needs occur (among them, control of dietary protein intake is recommended). In particular, specific nutritional needs have been highlighted to be relevant from the immune-metabolic point of view as well. For example, reduced intake of SFCAs (butyrate and propionate) or their reduced production by the gut microbiota may impair the downstream anti-inflammatory pathways, mediated by binding of SCFAs to metabolite-sensing G protein-coupled receptors (GPCR) [60]. Of note, as some of these receptors, e.g., GPR43, are expressed on the surface of different white cell subsets (neutrophils) and control their chemotaxis [61], the lack of SCFA intake or production in kidney disease can impact the activity of neutrophils and other immune cells [62]. ESRD is also characterized by the depression of the adaptive immune response, including the depletion of antigen-presenting DCs, naïve and memory T cells, reduced CD4/CD8 T cell ratio, and a diffuse B cell lymphopenia [63].

Finally, people with diabetes and diabetic kidney disease display reduced circulating levels of endothelial colony-forming unit precursors (CD34+/CD4+KDR+) and this finding is associated with worse cardiovascular outcomes in these patients [64]. However, it is unclear whether this decrease in circulating progenitor cells reflects a reduced proliferative capacity and activity of the hematopoietic compartment or if it is a consequence of the immuno-metabolic reprogramming of bone marrow cells in the setting of the increased systemic inflammatory burden.

Although an initial paradoxicali hyper-activation of the immuno-inflammatory response, a following state of immunosuppression occurs in later stages of CKD and ESRD, which might also be the result of the altered metabolism in CKD and ESRD patients.

Conclusions and Perspectives

Hyperglycemia and dyslipidemia correlate with the enhancement of the immuno-inflammatory response that can promote and worsen metabolic diseases. The identification of cellular checkpoints that modulate the immuno-metabolic machinery in the immune cells opens new avenues for purposing therapies to reprogram cellular metabolism and to finely tune functions of immune cells in the context of diabetes and its complications.

Compliance with Ethical Standards

Conflict of Interest   Fabrizia Bonacina and Andrea Baragetti declare that they have no conflict of interest.

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•• Of major importance

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