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HIGHLIGHTS

REVIEW

'Beauty and the beast' in infection: How immune–endocrine interactions regulate systemic metabolism in the context of infection

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The immune and endocrine systems ensure two vital functions in the body. The immune system protects us from lethal pathogens, whereas the endocrine system ensures proper metabolic function of peripheral organs by regulating systemic homeostasis. These two systems were long thought to operate independently. The immune system uses cytokines and immune receptors, whereas the endocrine system uses hormones to regulate metabolism. However, recent findings show that the immune and endocrine systems closely interact, especially regarding regulation of glucose metabolism. In response to pathogen encounter, cytokines modify responsiveness of peripheral organs to endocrine signals, resulting in altered levels of blood hormones such as insulin, which promotes the ability of the body to fight infection. Here we provide an overview of recent literature describing various mechanisms, which the immune system utilizes to modify endocrine regulation of systemic metabolism. Moreover, we will describe how these immune–endocrine interactions derail in the context of obesity. From a clinical perspective we will elaborate how infection and obesity aggravate the development of metabolic diseases such as diabetes mellitus type 2 in humans. In summary, this review provides a comprehensive overview of immune-induced changes in systemic metabolism following infection, with a focus on regulation of glucose metabolism.

Keywords: diabetes · glucose · infection · insulin resistance · metabolic disease

Introduction

Multi-cellularity of an organism allows for cells in the body to execute specialized functions. This is possible because the specialized function of some of these cells is to ensure the basic metabolic requirements for survival and function of all other cells. In organisms such as humans, metabolic requirements of cells are met by a carefully maintained homeostasis of nutrients, electrolytes and gasses. Homeostasis is controlled by the endocrine system; a vastly complex network of molecular interactions that communicates information such as nutrient levels to all organs. A dysbalance in homeostasis is detected by specialized receptors on sensory cells, which subsequently initiate an endocrine response, usually through excretion of small molecules called hormones. These endocrine signals, in turn, stimulate organ systems involved in regulation of the affected parameter to restore homeostasis. For example, in response to exercise, blood glucose levels drop, which is sensed by pancreatic α-cells. These, in turn, release glucagon

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in the blood stream, and this hormone stimulates the liver to increase gluconeogenesis and restore blood glucose levels back to baseline [1]. Some blood parameters, such as electrolytes, need to be tightly controlled between upper and lower limits to ensure survival, whereas others, such as glucose, have a relatively strict lower limit, but are allowed a higher level of upward fluctuation [2].

Few organ systems are as taxing to endocrine regulation of homeostasis as the immune system. Immune cells highly depend on glucose for their metabolism and in absence of major inflammatory incursions, the immune system is already responsible for nearly 20% of energy consumption. This may rise as high as 30% in case of infection [3, 4]. Following pathogen encounter, immune cells such as T cells rapidly proliferate and dramatically increase their total numbers in a few days. In addition, activated immune cells such as T cells, macrophages and NK cells switch from energy efficient oxidative phosphorylation to nutrient intensive glycolytic metabolism to meet their energetic needs [5]. These rapid changes in metabolism are mediated through a unique system of receptors and cytokines that function as immunological hormones. The immune system was therefore proposed to operate largely as an independent metabolic unit outside of normal endocrine control [6]. Endocrine-independent regulation of immune cell metabolism would make particular sense following infection, when a rapid response to pathogens takes priority over energy efficiency [4]. Nevertheless, the endocrine and immune systems regulate two vital functions, neither of which can be simply ignored by the other. Indeed, in recent years they have been shown to be tightly interwoven. Adipose tissue hormones, which communicate the status of nutrient stock availability, promote or inhibit the responsiveness of immune cells to activating stimuli in cases of nutrient abundance or shortage, respectively [7]. Conversely, cytokines are able to influence processes normally regulated by endocrine hormones, such as hunger, body temperature and glucose uptake, as well as production of endocrine hormones themselves [8–10]. Conversely, immune cells can respond directly to hormones such as insulin, which regulate systemic metabolism [9, 10]. Immune–endocrine interactions in the context of metabolic disease have been well studied. Surprisingly, the underlying physiology of these interactions have been largely ignored. Here, we will revisit recent data on the impact of the immune system on endocrine control in the context of infection, with a special focus on glucose homeostasis. The picture that emerges is that regulation of systemic metabolism is actively used by the immune system as a weapon against pathogens. Importantly, metabolic disease in the context of obesity appears to be partially dependent on derailed immune–endocrine interactions that normally contribute in the control of infection.

Immune–endocrine interactions in absence of infection

Upon activation, immune cells, especially T cells, switch towards energy-inefficient anabolic metabolism and glycolysis for the generation of ATP and building blocks for biosynthetic growth pathways [5, 11]. This high nutritional cost is justified by the protection it provides against a potentially lethal pathogen but should be reduced to a sustainable level in absence of infection. After pathogen clearance, redundant immune cells therefore die through apoptosis and remaining cells revert to catabolic metabolism, in particular oxidative phosphorylation, to support themselves [5]. The level of metabolic activity of resting immune cells, and thus their energy consumption, is subject to endocrine control. Conversely, tissue resident immune cells are important for the maintenance of tissue homeostasis and for guiding endocrine responses to changes in homeostasis as a result of infection, but also of metabolic stress [12].

Endocrine control of immune cell homeostasis

An important sensor of the general metabolic state of the organism is white adipose tissue (WAT). In time of nutrient abundance, adipocytes accumulate stocks of nutrients in the form of lipids, which are depleted when food sources are scarce. WAT communicates the levels of nutrient stocks to the body through the excretion of adipose hormones (also referred to as adipokines). Of these, the adipokines adiponectin and leptin have been most extensively characterized [13]. When the amount of lipids in adipose tissue decreases, for example during prolonged starvation, adipocytes excrete adiponectin to signal the body to reduce metabolic activity and increase energy efficiency [14]. In case of abundant nutrient availability, fat accumulates in adipocytes, which promotes excretion of leptin. Leptin signals satiety to the brain, by inhibiting sensitivity of neurons to ghrelin, a hormone that stimulates the feeling of hunger [14, 15]. Also, leptin inhibits lipogenesis and systemically increases the metabolism of glucose, thereby preventing lipid accumulation in adipocytes.

In addition, adiponectin and leptin control the function of the immune system [16]. Most immune cells express receptors for adiponectin, but these are particularly high on M2 macrophages [17]. Adiponectin promotes AMPK signaling and inhibits the NF-κB signaling cascade [18]. As a result, adiponectin inhibits the production of pro-inflammatory cytokines such as IL-6 and TNF and promotes production of anti-inflammatory mediators, such as IL-10 and IL-1Rα by macrophages and dendritic cells [19]. In addition, adiponectin was shown to directly inhibit responsiveness and functionality of T, B and NK cells [19–21]. Mice deficient for adiponectin demonstrate a hyper-reactive immune system. In humans, reduced adiponectin levels in circulation are associated with development of obesity, insulin resistance (IR) and diabetes mellitus type 2 (DM2) [22–24], as well as atherosclerosis, hypertension and vascular diseases [25].

Leptin, in contrast, has been associated with increased activity of the immune system. The receptor for leptin is expressed on both innate and adaptive immune cells, and is structurally and functionally homologous to the receptor for IL-6. Leptin promotes chemotaxis of neutrophils, stimulates development of NK cells and enhances production of IL-6 and TNF by macrophages [26]. In T cells, leptin stimulates survival and proliferation, as well

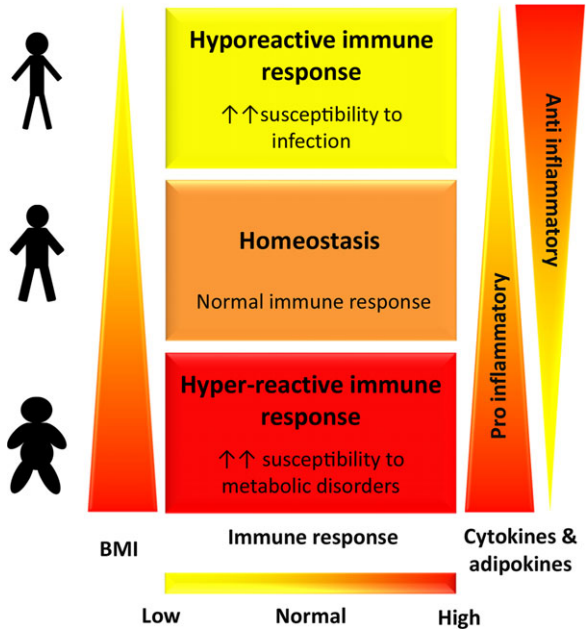

Figure 1. Immune endocrine interactions during starvation and obesity. Adipose tissue contains the nutrient stocks of the body in the form of triglycerides. It communicates its contents to the body through the excretion of adipokines such as adiponectin and leptin, which signal low or high amounts of these stocks, respectively. These hormones also impact the functionality and therefore nutrient consumption of the immune system. Whereas adiponectin limits immune cell functionality, leptin brings them in a higher state of activity. During prolonged starvation, increased adiponectin levels induce hypo-activity of the immune system thus rendering the organism susceptible to infection. In obesity, high levels of leptin contribute to the hyperreactivity of immune cells, which promotes development of metabolic disorders. BMI = Body Mass index.

as enhanced production of pro-inflammatory cytokines such as TNF and IL-6 via the JAK3/STAT3 signaling pathway [27, 28]. Mice deficient for leptin or its receptor develop severe obesity but also demonstrate a strong reduction in their number of circulating T cells, NK cells and dendritic cells [29]. In humans, leptin levels are strongly increased in people with obesity, and the levels of this hormone in the blood are positively correlated with pro-inflammatory cytokines, phagocytosis and enhanced Th1 responses [15, 30]. In summary, in absence of infection, the general state of readiness of the immune system, and therefore its nutrient consumption, is impacted by endocrine hormones that reflect the nutrient availability of the organism (Fig. 1).

Immunological control of endocrine signaling

Immune cells also affect endocrine regulation of metabolism even in absence of infection [31]. Most tissues are populated by 'homeostatic' immune cells, such as M2 macrophages, ILC2s, eosinophils and regulatory T cells. These cells are important for preventing aberrant immune activation and tissue damage as a result of inflammation [32, 33]. In addition, cytokines produced by these cells, which are typically of a Type-2 profile, affect nutrient uptake by non-immune cells. Animals deficient for eosinophils or IL-5 demonstrate increased adipose tissue mass following an obesity-inducing diet [32, 34].

In addition, the immune system plays a key role in the development of diet-induced metabolic disease, such as DM2 and non-alcoholic fatty liver disease [7, 35, 36]. Obesity is commonly associated with insulin resistance which can progress towards DM2 [37]. An important underlying cause of IR is chronic systemic inflammation. Pro-inflammatory cytokines, such as TNF and IL-1β reduce the signal transduction capacity of the insulin receptor on insulin-sensitive tissues through modification of its intracellular signaling components [38–40]. Reduction of inflammation in mice, for example through TNF deficiency [38, 41] therefore significantly reduces development of IR in the diet-induced obesity (DIO) model. Obesity-induced inflammation is thought to originate in visceral adipose tissue (VAT) [39, 40] and experimental excision of VAT in mice fed with HFD indeed strongly delays development of IR [42]. In lean adipose tissue, the dominant immune cells are macrophages [39, 43]. In mice fed with normal chow diet (NCD) these cells have the phenotype of anti-inflammatory or M2 macrophages that produce Th2 cytokines such as IL-4 and IL-13. Through interactions with other tissue resident anti-inflammatory immune cells, such as eosinophils, NKT cells and ILC2 cells, M2 macrophages maintain adipose tissue homeostasis and prevent development of IR [7]. DIO induces conversion of macrophages to a pro-inflammatory M1-like phenotype [44]. Obesity drives the local production of a number of pro-inflammatory stimuli in VAT, such as leukotrienes produced by obese adipocytes, cellular debris from necrotic adipocytes, and cytokines produced by NK cells activated by metabolically stressed adipocytes [42, 45, 46]. These factors induce M1-polarization of macrophages, which subsequently produce high levels of TNF and IL-1β. Release of these cytokines in circulation promotes development of IR [7]. Thus, the immune system has an important impact on endocrine signaling also in absence of infection.

Regulation of blood glucose levels during infection

Infection presents the host with a difficult dilemma: on the one hand it needs to increase its metabolism to allow the immune system and innate defense mechanisms of non-immune cells to optimally function [3, 47]; on the other hand, it needs to restrict nutrient availability to the pathogen [48, 49]. Many studies have shown that pro-inflammatory cytokines such as TNF, IL-1β and IFNγ increase insulin resistance (IR) in the context of obesity-induced chronic systemic inflammation [50]. Infection may induce loss of glycemic control, resulting in either hypo- or hyperglycemia (dysglycemia), yet this is relatively rare and generally the result of severe infections such as those that develop sepsis [51]. Rather, many infections induce only IR without changes in either fasting or postprandial blood glucose levels (euglycemia). Recent data indicate that the purpose of immune-mediated regulation of systemic metabolism is to restrict access of pathogens to nutrients, whilst

simultaneously allowing optimal immune cell function. Importantly, the level of infection impacts the degree to which systemic metabolism is affected. Below, we will discuss the molecular mechanisms and physiological relevance of these various mechanisms.

Euglycemic hyperinsulinemia

Cytokine-induced systemic insulin resistance without changes in blood glucose levels appears to be relatively common and occurs even after mild infections. An analysis of patients infected with HIV showed increased insulin levels, whereas fasting plasma glucose levels (FPG) were not different from those of age and gender-matched controls [52]. Similarly, people with acute mild respiratory infection showed higher insulin levels, but similar blood glucose levels at time of diagnosis compared to a time point three months later [10]. In mice, infection with cytomegalovirus (CMV), lymphochriomeningitis virus (LCMV) or mild influenza, induced systemic insulin resistance, whereas it did not lead to a loss of glycemic control [10]. In lean people and mice, infection-induced IR is compensated by increased insulin output by the pancreas, which prevents fasting and postprandial hyperglycemia [10].

Increased blood glucose levels therefore do not appear to be the purpose of infection-induced insulin resistance. Instead, it was proposed that by inducing insulin resistance, inflammatory mediators redirect nutrients such as glucose from the liver and muscle to the immune system [6]. However, IR by itself does not automatically lead to increased systemic nutrient availability. During fasting, the majority of glucose uptake is mediated through insulin-independent mechanisms [53, 54]. Organs such as the muscle have mechanisms in place to increase glucose uptake even when blood glucose and insulin levels are low, for example during exercise [55]. In addition, whereas muscle takes up most glucose from the bloodstream after feeding and part of that glucose is stored as glycogen, the majority of carbon molecules from glucose are returned to the bloodstream in the form of lactate [54]. In fact, many organs use carbon metabolites other than glucose, such as lactate and short chain fatty acids, as their primary energy source, both in the presence and absence of insulin [54, 56]. Organs which are critically dependent on glucose for survival, such as the brain but also the immune system, express high-affinity glucose transporters, allowing them to take up glucose from the blood, even when its levels are low [57]. The primary role of postprandial insulin production therefore appears to be preventing hyperglycemia-induced tissue damage rather than controlling resource allocation. Moreover, increased pancreatic insulin production compensates for infection-induced IR in muscle and liver, meaning that the majority of postprandial glucose is still taken up by these organs. Thus, direct resource re-allocation is not likely to be the purpose of infection-induced insulin resistance.

Rather, the benefit of infection-induced IR appears to be its compensatory hyper-insulinemia. In addition to regulating blood glucose uptake, insulin is a key signaling molecule with regards to nutrient usage. Whereas the majority of insulin-induced glucose uptake is executed by skeletal muscle, this hormone has receptors on almost all cells in the body [58]. Insulin is a signal of acute nutrient availability and is therefore a signal to most organs to change fuel sources and increase anabolic metabolism. For example, in response to insulin, the heart stops using β-hydroxybutyrate as a carbon source and switches to pyruvate, lactate and glucose [54, 56]. In muscle and liver, insulin promotes glycogenesis and protein synthesis, whereas in adipose tissue and liver insulin promotes lipogenesis. The immune system has its own receptor and ligand system that regulates functional and metabolic activity. However, the intracellular components used by these receptors converge on the same downstream molecular signal transduction systems as those of the endocrine system. For example, both the co-stimulatory molecule CD28 on T cells and the insulin receptor converge on PI3K for their signal transduction [59, 60]. As a result, both CD28 stimulation and insulin receptor triggering result in glucose transporter upregulation and induction of anabolic metabolism [59, 61, 62]. Yet immune cells are not impervious to endocrine control and two recent papers using murine models have shown that insulin plays a prominent role in anti-viral T cell responses [9, 10]. Activated $CD4^+$ and $CD8^+$ T cells induce expression of the insulin receptor and its stimulation during priming promotes proliferation, cytokine production and cytotoxicity of these cells. T cell specific deletion of the insulin receptor increased lethality after influenza infection in mice, whereas it reduced pathology in a CD4 T cell dependent model of colitis [9]. Moreover, injection of basal insulin during cytomegalovirus infection increased the anti-viral CD8 T cell response [10]. Finally, by preventing infection-induced hyperinsulinemia, either through elimination of pancreatic β-cells or by blocking cytokine-induced insulin resistance, the anti-viral CD8 T cell response following viral infection was reduced [10]. Insulin was only able to boost T cell activation in the presence of CD28 co-stimulation and therefore mimics the function of pro-inflammatory cytokines [10]. This provides a clue towards the physiological role of insulin-mediated co-stimulation: Whereas cytokines are mostly produced by specialized immune cells in lymph nodes or at the site of infection, insulin is constantly and systemically present. Insulin-mediated stimulation may therefore operate at times when T cells encounter lower concentrations of cytokines, such as during migration through the blood stream.

Insulin-mediated regulation of metabolism in response to feeding represents a highly efficient strategy for dealing with nutrient availability which has been conserved from insects to man [63]. Modifying this system is therefore a tactic that is not without risk, as it touches on a vital function for normal physiology. In case of pathogen encounter this is justified as it may prevent potentially lethal infection. The immune system has been shown to impact insulin-signaling at various levels. IL-1β derived from macrophages directly promotes postprandial insulin production by pancreatic β-cells [64]. This is surprising, as increasing insulin levels without affecting systemic insulin sensitivity carries the risk of inducing life-threatening hypoglycemia. In response to infection, systemic levels of IL-1β can go up over 100-fold [65] and currently it is unclear how this impacts insulin production. One explanation may be that in parallel, pro-inflammatory

cytokines including IL-1β, TNF and IFN-γ target systemic insulin sensitivity [42, 66, 67]. In the context of infection, IFN-γ has been shown to specifically inhibit insulin sensitivity in skeletal muscle by downregulating the insulin receptor, causing reactive hyperinsulinemia. Genetic ablation of the IFN-γ receptor on myocytes prevented systemic insulin resistance and reactive hyperinsulinemia, but also impaired effector CD8 T cell responses following viral infection [10]. Notably, hepatic insulin sensitivity was not reduced during infection and fasting plasma glucose levels were therefore not affected. This again indicates that changes in euglycemia are not a direct goal of immune-mediated changes in insulin-biology. Currently it is unclear how an increase in systemic insulin does not lead to reduced fasting plasma glucose levels, but this may be the result of a compensatory increase in glucagon production of pancreatic α-cells.

Interestingly, a recent paper demonstrated that insulin resistance can increase glucose levels in the jejunum, because of impaired glucose uptake [68]. Increased nutrient availability in the gastrointestinal tract of mice infected with a lethal dose of *C.Rodentium* resulted in reduced expression of virulence factors by this pathogen and decreased death [68]. In these experiments, IR was actively induced in mice through iron overload. It is therefore currently unclear whether changes in the gastrointestinal nutrient composition are actually occurring under physiological conditions and are an active strategy of infection-induced IR. Nevertheless, this study does illustrate that immune-mediated changes in systemic metabolism can be used to fight infection at multiple levels.

In summary, infection-induced insulin resistance appears to have evolved primarily to benefit from the pro-anabolic effects of increased systemic insulin levels (Fig. 2).

Infection, anorexia and low blood glucose

Anorexia is a relatively common effect associated with infection. Upon pathogen encounter, systemic release of cytokines such as IL-1β, TNF and IL-6 promote release of leptin by adipocytes to reduce hunger [69]. In addition, these cytokines directly impact the central nervous system of humans and mice in order to reduce food intake [70, 71]. Finally, cytokines such as TNF, IL-6 and prostaglandins promote nausea and vomiting, which further reduces food intake [72]. Anorexia following infection is a process that is conserved from fruit flies to humans and was therefore proposed to be of importance for the host defense against pathogens. Surprisingly, experimental evidence for the beneficial effects of anorexia are limited. Low nutrient intake was shown to increase survival of *Drosophila* infected with *S.typhimurium*, whereas it was detrimental after infection with *L.monocytogenes* and had no influence on pathogenesis of *E.faecalis* [73]. In mice, low nutrient intake protected against *L.monocytogenes* [74], whereas it sensitized for pathology following infection with *Candida albicans*, *S.typhimurium*, Influenza and *H.bakeri* [75–77]. In humans, low blood glucose levels are associated with worsened outcome after sepsis [47] and clinical guidelines therefore recommend enteral or parental feeding of critically ill patients [78].

It is important to note that anorexia does not cause hypoglycemia. In previously well-fed organisms, even prolonged fasting does not lead to reduced systemic glucose availability below a threshold value that is already reached several hours after feeding [79]. Upon fasting, nutrient stores in liver and adipose tissue are converted back to glucose through hepatic gluconeogenesis and glycogenolysis, which ensures a fasting plasma concentration of around 5 mmol/l [79]. The biggest impact of anorexia on physiology is therefore not the ability of organs to access nutrients. Rather it affects the metabolic state of the organism. Hormones such as insulin, growth hormone and IGF-1, which are produced after food intake, do not only signal organs to take up glucose, but also to use these nutrients for anabolic metabolism. In the absence of these signals, cells in the body revert to an energy-preserving state. Cells switch their metabolism towards the use of glucose metabolites and short chain fatty acids as their primary energy source and reduce their anabolic processes [54, 56]. Pathogens like cytomegalovirus increase nutrient uptake in infected cells [80] and viral replication is impaired in case of nutrient restriction [81]. Thus, rather than limiting glucose availability, infection-induced anorexia appears to reduce nutrient uptake by peripheral cells in order to limit its availability to pathogens.

The one cell system that should not restrict its anabolic metabolism in time of infection is the immune system. As mentioned, under homeostatic conditions immune cells are subject to endocrine control by hormones such as adiponectin, which limit their nutrient use [17]. In time of infection, activated immune cells such as T cells and macrophages switch from predominantly oxidative to primarily glycolytic metabolism [5]. This is possible, because infection presents the body with an acute threat which causes the release of cytokines and upregulation of co-stimulatory molecules that release immune cells from normal endocrine control. For example, in response to CD28 ligands on activated dendritic cells, T cells highly upregulate the glucose transporter GLUT1, allowing their full activity at glucose concentrations as low as 0.5 mmol/l [61, 62]. Thus, the immune system is able to operate at maximal efficiency even if the rest of the body is in a mode of nutrient preservation following starvation. In addition, recent evidence indicates that immune cells may in fact benefit from infection-induced fasting. Whereas effector CD8 T cells depend on glycolysis for their optimal function, memory cells revert to oxidative phosphorylation to fulfill their energetic needs [82]. Short chain fatty acids, which are produced in high abundance following fasting, are converted to Acetyl-CoA and directly feed into the citric acid cycle [54, 56]. Acetate, which is converted in Acetyl-CoA in a single step, was therefore shown to promote both memory CD8 T cell metabolism and function [83]. Even though infection-induced anorexia was not directly shown to promote memory CD8 T cell formation by increasing circulating ketone bodies, this possibility indeed seems likely.

In contrast to anorexia, infection-induced hypo-glycemia, when blood levels drop below 3 mmol/L [84], is a rare event. Nevertheless, hypoglycemia has been reported following infection with a large number of different pathogens, including malaria, *B.pertussis*, mumps, *C.albicans* and sepsis [51, 85–87]. The

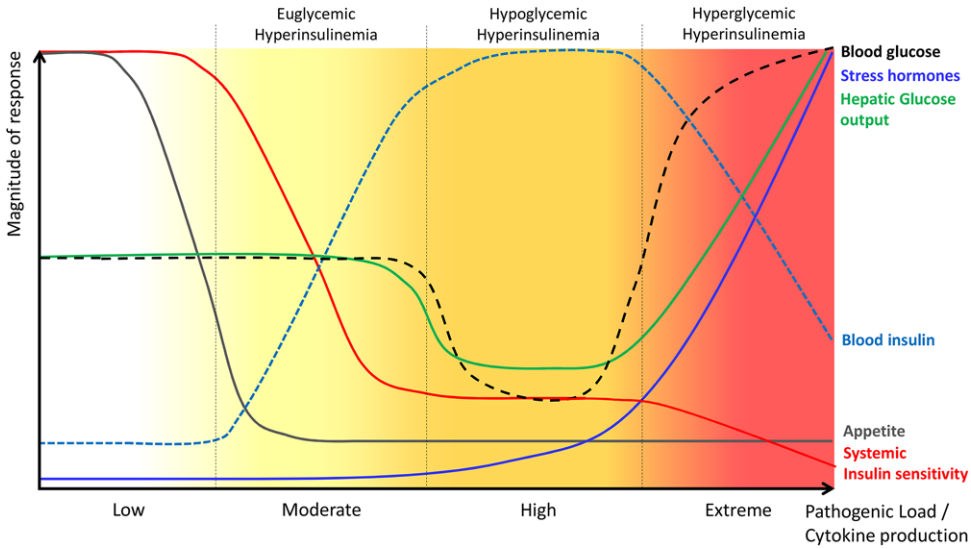

Figure 2. The severity of infection determines the degree of changes in endocrine control of blood glucose. During the majority of infections, when pathogenic loads and the cytokine response are low to moderate, cytokines such as IFN-γ induce mild insulin resistance in muscle and a compensatory increase of pancreatic insulin production. This state of hyper-insulinemic euglycemia (yellow area) boosts the immune system but does not result in changes in blood glucose levels. At high pathogenic loads, cytokines such as TNF and IL-1β boost pancreatic insulin production beyond what is required to sustain blood glucose homeostasis. This lowers hepatic glucose output and causes hypoglycemic hyperinsulinemia (orange area) brings the whole body in a heightened state of awareness for infection and limits nutrient availability to pathogen. At very high, life-threatening levels of infection such as during sepsis, cytokine storms cause an acute production of adrenal stress hormones. These molecules inhibit pancreatic insulin production and boost hepatic glucose production, in order to generate a state of systemic hyperglycemia (red area) aimed to preserve functionality of vital organs such as the brain and hart. (gray line) Appetite, (Red line) systemic insulin sensitivity, (dashed blue line) blood insulin levels, (green line) hepatic glucose output, (dark blue line) adrenal stress hormones, (dashed black line) blood glucose levels.

immune system also plays a role in the induction of hypoglycemia, through the excretion of cytokines. Experimental models have shown that injection of high levels of IL-1α, IL-1β, TNF or LPS induce hypoglycemia in mice [88]. Infection-induced hypoglycemia is generally associated with hyperinsulinemia, indicating that these cytokines enhance insulin output by the pancreas. Indeed, IL-1β has been shown to directly stimulate pancreatic β-cells to produce insulin [64]. The physiological role of infection-induced hypoglycemia is still unclear. It has been proposed that low blood glucose levels limit ROS production in the brain and therefore reduce chances for neuronal damage [89]. However, since hypoglycemia itself presents a real danger for induction of brain damage, coma and even death [84], this is a very risky strategy and additional roles for this process therefore appear likely. We hypothesize that hypoglycemia brings the body in a general state of stress in order to potentiate responsiveness to infection. Clearly, infection-induced hyper-insulinemic hypoglycemia is a high-risk strategy, only used in situations of high pathogenic load when conventional strategies are insufficient to clear the pathogen.

Infection and stress hyperglycemia

Under conditions of severe stress such as physical trauma, major surgery or during sepsis [90], blood glucose levels may rise above physiological levels in a process called stress hyperglycemia. Stress hyperglycemia is a process conserved from insects to vertebrates [91]. Severe stress activates a neuroendocrine response, resulting in the release of the hormones epinephrine, norepinephrine and cortisol [91]. These molecules strongly promote gluconeogenesis by the liver and together with IL-1β, TNF and IL-6 promote insulin resistance in hepatocytes and cells from the skeletal muscle [92]. Simultaneously, insulin production by pancreatic β-cells is reduced, resulting in a dramatic rise of blood glucose levels [93]. Originally it was thought that stress hyperglycemia is detrimental for patients [94]. However, the NICE-SUGAR multi-center prospective study revealed that patient submitted to the ICU with hyperglycemia showed an increased mortality rate after intensive regulation of blood glucose levels compared to controls [95]. It is currently believed that hyperglycemia is induced to ensure that sufficient levels of glucose reach vital organs under conditions of reduced blood flow, such as after an ischemic insult or during septic shock [91]. Various studies have shown that high glucose concentrations protect against pathological insults, such as hypoxia and apoptosis, whilst promoting angiogenesis [91]. However, prolonged hyperglycemia is detrimental as it promotes apoptosis in cardiomyocytes and kidney cells [96, 97]. Moreover, stress hyperglycemia predisposes people for the development of metabolic diseases such as diabetes mellitus type 2 later in life [98]. Thus, stress hyper-glycemia presents a 'last-resort' strategy that preserves glucose availability to vital tissues at a price of long-term damage to peripheral organs.

In summary, whereas changes in endocrine regulation of metabolism are common in response to infection, alterations of systemic glycemia are rare and only appear to occur during severe

infections, when less detrimental strategies are insufficient to clear the pathogen.

Infection and diabetes

Infection and diabetes: A clinical perspective

DM2 is a chronic progressive metabolic disease defined by an impaired ability to maintain fasting or postprandial blood glucose levels below defined threshold values. People with DM2 often suffer from serious co-morbidities, such as heart failure, renal insufficiency, brain stroke and blindness. It is a growing global health problem with estimated 425 million affected people in 2017 and 629 million in 2045 [99]. In contrast to Diabetes mellitus type 1 (DM1), which is caused by an autoimmune process directed to β-cells/insulin, DM2 is associated with unhealthy life styles, such as excessive nutrient intake, a sedentary life style and obesity. However, increasing evidence indicates that infection may be a risk factor for the development of DM2, especially in people predisposed for development of metabolic dysfunction. People with diabetes, both type 1 and type 2, are well known to be more susceptible for infections and inflammatory disease [100]. Prospective epidemiological studies have confirmed that a higher fraction of glycated HbA_{1C}, a clinical measure for reduced glycemic control, increases the risk of infection [101]. For example, a greater fraction of patients with DM2 are infected with cytomegalovirus, *Helicobacter pylori* or tuberculosis than control subjects [102–104]. Also, inflammatory diseases, such as psoriasis, colitis and vasculitis are positively correlated with the occurrence of DM2 [105]. These observations make it difficult to interpret epidemiological data on the causal relationship between chronic infections and diabetes, i.e. whether they are the cause or a result of DM2. Because of this, infection is currently not recognized by clinical guidelines as a risk factor for the development of DM2 [84]. Adenovirus 36 (Adv36) infection has been positively correlated with obesity [106] and it was shown that several of its genes directly stimulate adipogenesis and lipogenesis [107]. Surprisingly, Adv36 is uncommon in patients with DM2 and is associated with increased insulin sensitivity [108]. The only chronic infectious agent that can be directly linked to the onset of DM2 is hepatitis C [109]. Patients infected with hepatitis C virus (HCV) have a strongly increased prevalence of diabetes mellitus type 2 [110–112]. HCV infects hepatocytes and directly impacts insulin sensitivity in these cells, thus dysregulating the ability of the liver to control blood glucose levels [113, 114]. In addition, HCV infection causes lipid accumulation in liver and may lead to fibrosis, cirrhosis and hepatocellular carcinoma in patients [115–117]. Current estimates suggest over 70 million people to be chronically infected with HCV, making it an important risk factor for the development of both liver disease and DM2 [118].

The link between acute infection and development of DM2 is much less well studied than that of chronic infection, but various small-scale research initiatives indicate that a causal relationship may exist. Prospective studies show that the diagnosis of diabetes mellitus type 2 is typically preceded by a period of years to decades in which systemic insulin resistance gradually increases. This stage is normally not associated with major clinical symptoms as it is compensated by increased pancreatic insulin output and is therefore referred to as 'pre-diabetes' [119, 120]. In contrast, the onset of DM2 is usually associated with an abrupt increase of blood glucose levels, overwhelming the ability of pancreatic cells to sustain euglycemia [119, 120]. It was therefore proposed that an acute stress factor is associated with the transition of pre-diabetes to DM2 [10]. Indeed, severe stress, such as perceived psychological stress, but also infection often precedes development of DM2 in high-risk groups, especially if it is associated with high blood glucose levels at first presentation of disease [119, 121]. Infection has therefore been included in guidelines for diabetes care as a cause of acute diabetic events, such as ketoacidosis [84]. Nevertheless, scientific evidence for the causal link between infection and DM2 is limited. Various studies in the eighties and nineties of the previous century showed that acute infection, both of bacterial and viral origin, is associated with an increase in systemic insulin resistance [122–124]. Our group recently confirmed these findings in a small cohort of patients with acute respiratory infection [10]. Whereas human studies using hyper-insulinemic euglycemic clamping showed that, even though the infection-induced effects on blood glucose regulation were transient, insulin resistance was typically retained for at least one month after recovery and was prolonged in patients with a higher BMI [124]. Whether acute infection is capable of pushing patients with pre-diabetes towards DM2 could not be concluded from these relatively small-scale studies, even though patients that had been critically ill from bacterial infection were shown to be at higher risk of developing DM2 later in life [98].

A hypothesis that has gained some traction is recent years is that of the 'leaky gut' syndrome. Obesity and diabetes are associated with alterations in the microbial gut flora [125]. In addition, it was shown that in humans, diabetes type 2 is accompanied by increased permeability of the intestines [126]. It was therefore proposed that a constant influx of microbes and endotoxins into the blood stream contributes to the chronic systemic inflammation observed in patients with DM2 [127]. Indeed, endotoxemia is higher after a meal than during fasting in healthy non-diabetic men [128], which was shown to be increased in the context of obesity and diabetes [129, 130]. The level of postprandial endotoxemia also depended on the type of nutrients consumed, suggesting that an unhealthy life-style had a particularly negative impact on patients with DM2 [129, 130]. Whereas studies into leaky gut syndrome mostly focused on endotoxins, the underlying immunological responses to these compounds are mostly similar to those activated in response to a 'regular' infection, albeit at lower intensity [127]. Thus, both severe acute and low-grade chronic infection appear to contribute to the general receptiveness of people with pre-diabetes to the development of DM2.

In summary, because DM2 predisposes people for infection, the impact of infection on development of DM2 has so far been occluded in epidemiological studies. Nevertheless, there is extensive clinical evidence that both acute and chronic infection

negatively impacts insulin sensitivity and may therefore be an important risk factor for patients with pre-diabetes to develop DM2.

Infection and diabetes: A molecular perspective

To understand on a molecular level how infection contributes, or even synergizes with the pathophysiological processes that underlie development of DM2, one needs to consider the various levels at which metabolic disease leads to loss of glycemic control. Three main organs are primarily responsible for glucose uptake following insulin excretion, i.e. skeletal muscle, liver and WAT and in DM2 typically all of these organs display IR. As a direct result, not only blood glucose uptake is reduced, but also muscle and liver store less glucose in the form of glycogen, the liver produces more glucose through gluconeogenesis during fasting and adipose tissue has impaired suppression of lipolysis, which all contribute to systemic hyperglycemia [131]. In addition, mechanisms of IR differ per organ and not all signaling cascades within cells are equally affected. For example, in liver cells insulin resistance is associated with impaired PI3K/Akt signaling, resulting in increased gluconeogenesis, whereas SREBP1c activation by the insulin receptor is preserved, causing an accumulation of lipids in these cells [36]. On top of that, dysfunction of other tissues than liver, muscle and WAT further contributes to disease. For example, pancreatic dysfunction leads to decreased insulin production and a relative increase of glucagon excretion by α-cells. Also, increased glucose resorption in the kidney, decreased incretin secretion by the gut and insufficient suppression of satiety in the central nervous system contribute to the pathogenesis of DM2 [132]. The activated immune system, as well as various pathogens appear to aggravate many of these processes. An exhaustive review of all molecular interactions involved in IR is beyond the scope of this manuscript and has been excellently reviewed elsewhere [50], but we will provide examples of the most important players below.

The insulin receptor (INSR) is a ligand-activated tyrosine kinase transmembrane protein containing several phosphorylation sites for the binding of adaptor molecules [131]. Proximal signaling is predominantly executed by the Insulin Receptor Substrate (IRS) family of proteins, which contains 6 members of which IRS1 and IRS2 mediate the majority of metabolic effects. IRS molecules contain over 70 activating and inhibitory phosphorylation sites that mediate the recruitment of additional molecules for signal transduction. The INSR/IRS complex activates major signaling pathways such as the PI3K and Ras/ERK mediated signaling cascades [133]. IR is the result of changes in various molecular players involved in INSR signaling, many of which are affected by infection [131]. A molecule directly involved in the negative regulation of insulin sensitivity is IFN-γ. IFN-γ produced in response to pathogens such as mCMV, LCMV and influenza directly targets skeletal muscle to downregulate expression of the insulin receptor, resulting in systemic IR, but not glucose intolerance in lean mice [10]. In contrast, in animals with diet-induced hepatic, but not yet systemic insulin resistance, infection resulted in the long-term development of glucose intolerance and aggravation of diabetic nephropathy [10].

Inflammation also affects the interaction between the INSR and its adaptor molecules, most notably IRS1 and IRS2. Various types of cellular stress factors associated with infections, such oxidative stress and ER stress lead to the activation of c-Jun NH2-terminal kinase (JNK) and IκB kinase beta (IKKβ) which directly mediate inhibitory phosphorylation of IRS1 [134, 135]. In addition, they mediate upregulation of stress-ligands and excretion of soluble mediators that can attract and activate pro-inflammatory immune cells [7]. These cells produce cytokines, such as TNF-α and IL-1β, which are potent activators of JNK and IKK-β, thus leading to further inhibition of IRS molecules [136–138]. Pathogens can also directly target proximal insulin receptor signaling. HCV causes downregulation of IRS1 in liver through interaction of viral protein NS5A with CD2-associated protein (CD2AP) which in turn activates casitas B-cell lymphoma (Cbl/Cbl-b) E3 ligase to degrade IRS1 [139]. Proximal INSR signaling is further affected by the suppressor of cytokine signaling (SOCS) family of proteins. Many cytokines such as IL-6 and IFN-γ, but also the adipokine leptin induce expression of SOCS molecules through the activation of JAK/Stat signaling [140]. SOCS, in turn, bind tyrosine kinase receptors, inhibit activation of JAK and Tyk2 molecules and mediate receptor degradation. SOCS molecules are therefore part of a classical negative feedback-mechanism in cytokine signaling [140]. The effects of SOCS molecules reach beyond that of JAK/Stat signaling. SOCS-1 and SOCS-3 have been shown to inhibit insulin receptor phosphorylation [141]. Moreover, SOCS-1 and -3 are able to directly mediate ubiquitination and subsequent degradation of IRS1 and IRS2 molecules [142]. Indeed, in response to IL-6, human cells induce SOCS molecules, which impairs their sensitivity to insulin [143]. Overexpression of SOCS molecules in hepatocytes induced insulin resistance in mice, whereas their inhibition improved sensitivity to insulin in obese *db/db* animals.

With regards to the impact of pro-inflammatory cytokines on distal insulin receptor signaling, AMP-activated protein kinase (AMPK) has been studied most extensively. AMPK is a key energy and nutrient sensor in the cell [144]. When nutrient levels are low, the amount of AMP in the cell increases, which activates AMPK. Activated AMPK promotes transcription and translocation of glucose transporters and promotes catabolic metabolism, such as increased glucokinase activity, glycolysis and fatty acid oxidation (FAO). Simultaneously, it inhibits mTORC1, a signaling nexus that promotes anabolic metabolism. AMPK is therefore a key signaling molecule in the regulation of muscle metabolism and hepatic glucose production and is normally inhibited by insulin. Various cytokines have been shown to target AMPK signaling [145]. Treatment of mice with TNF results in the upregulation of the phosphatase PP2C, a negative regulator of AMPK. As a result, animals showed reduced levels of the AMPK downstream target Acetyl-CoA carboxylation (ACC), reduced fatty acid oxidation, increased intramuscular DAG accumulation and reduced sensitivity of skeletal muscle to insulin [146]. Neutralization of TNF or genetic ablation of the TNF receptor in obese (*ob/ob*) mice

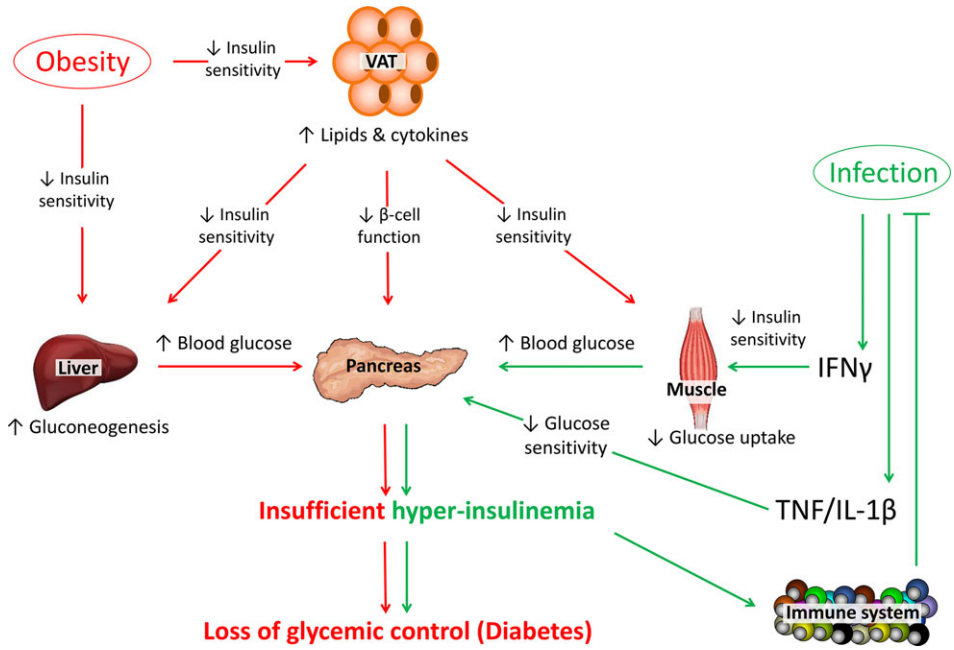

Figure 3. In obesity, metabolic and immunological signals synergize to promote insulin resistance. In response to obesity (red text/arrows), the increase of lipids and cytokines in endocrine organs and in circulation reduce insulin sensitivity, boost systemic glucose levels and promote pancreatic insulin production. Following infection (green text/arrows) the immune system produces cytokines such as IFN-γ, TNF and IL-1β which also reduce systemic insulin sensitivity and increase pancreatic insulin output. When obesity and infection coincide, the ability of the pancreas to compensate systemic insulin sensitivity may be overwhelmed, leading to development of diabetes mellitus type 2.

reversed the inhibitory effects of metabolic disease on AMPK signaling. AMPK is also a direct target of many pathogens [147]. HCV, adenovirus, and Epstein-Barr virus were shown to inhibit AMPK phosphorylation in hepatocytes, causing reduced fatty acid oxidation and lipid accumulation [148, 149]. Activation of AMPK by metformin, a drug widely used in treatment of DM2 to ameliorate metabolic parameters, was shown to reduce viral replication in hepatocytes [150]. Conversely, pathogens such as hepatitis B virus [145, 151, 152], cytomegalovirus and vesicular stomatitis virus are known to activate AMPK. In addition to viruses, various bacteria, such as *S. typhimurium* and *M. tuberculosis* [153, 154] inhibit AMPK and infection with the latter has indeed been positively correlated with DM2 in humans [155].

Finally, infection negatively impacts systemic insulin sensitivity through modification of metabolites in circulation, most notably lipids such as ceramides. Ceramides are sphingolipids that are formed from serine and acyl-CoA, particularly palmitoyl-CoA. Ceramides C18 and C16 accumulate in muscle, liver, and WAT of obese humans and rodents [156]. Ceramides interfere both with proximal INSR signaling [157] and with downstream activation of AKT by promoting activation of protein phosphatase 2A (PP2A) [158] and PKCζ [159], as well as inhibiting direct phosphorylation of Akt on Ser^{473} phosphorylation [160]. Infection with both viral and bacterial pathogens has been shown to increase ceramide levels [161, 162], which is involved in the development of pathology [162]. Interestingly, whereas infection increases ceramide levels and ceramides negatively impact insulin sensitivity, it has not been formally proven that infection causes systemic IR through an increase of specific forms of ceramides.

In summary, infection targets many of the intracellular signaling cascades that are also dysregulated in metabolic dysfunction. As a result, obesity and infection appear to synergize with each other in the induction of insulin resistance (Fig. 3). Whereas infection is currently not recognized as a risk factor for the development of DM2 [84], molecular evidence indicates that a causal relationship is highly likely.

Conclusion

The endocrine and immune systems control distinct functions in a multicellular organism that at first glance seem independent. Whereas the endocrine system ensures systemic homeostasis, the immune system provides protection against infection. However, during evolution, several feedback loops have developed between these systems that coordinates an organism-wide response to infection. In order to study these interactions, it is necessary to challenge each of the systems to provoke a dysbalance in these feedback loops. Unfortunately, this makes it difficult to study immune–endocrine interactions in humans, but many of the underlying molecular mechanisms appear to be highly conserved, allowing the use of animal models. Nevertheless, the vital function of the endocrine system in regulation of systemic metabolism, as well as functional redundancy of regulatory elements of both the immune and endocrine systems requires for advanced cell-specific systems to question functionality of specific models even in murine models.

Several major research questions are therefore still open. Which key molecular events trigger the transition from euglycemia to hypo- or hyperglycemia in infection? The central nervous system (CNS) plays a crucial role in regulation of systemic metabolism and inflammatory mediators increase resistance of this organ to insulin and leptin. How does infection impact central regulation of metabolism and how does this contribute to the fight against pathogens? Which immunological factors are involved in the loss of the ability of the pancreas to compensate for systemic insulin resistance during the development of diabetes mellitus type 2? We and others have shown that insulin promotes immune cell

function, at least in lean animals. However, people with DM2 generally display hyperinsulinemia, but are well known to have immune cell dysfunction. Thus, chronic hyperinsulinemia appears to have a different impact on the immune system than an acute, transient increase of this hormone in the blood and how this is regulated is currently unknown.

With a progressively obese global population, these questions are of increasing importance for the general wellbeing of our society. Whereas infectious diseases are no longer a major cause of death in the western world, its impact on public health continuous to be highly relevant. Further research how the elegant system of endocrine control ('the beauty') unleashes 'the beast' of the immune system during infection, therefore promises to provide new insights into the development of DM2 as well as provide leads for its treatment.

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