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Immunometabolism: an emerging frontier

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Abstract

Immunometabolism is an emerging field of investigation at the interface between the historically distinct disciplines of immunology and metabolism. Accelerating interest in this area is being fueled by the obesity epidemic and the relatively recent realization first that obesity impacts the immune system and promotes inflammation, and second that obesity-induced inflammation potentially promotes a variety of chronic conditions and diseases. The multi-level interactions between the metabolic and immune systems suggest pathogenic mechanisms that may underlie many of the downstream complications of obesity and offer substantial therapeutic promise.

"To lengthen thy life, lessen thy meals."

Benjamin Franklin, Poor Richards Almanac, 1737

It has long been recognized that effector cells of the immune system are required to ward off tumours and infectious agents. Likewise, it is well known that regulatory cells of the immune system rein in such responses, as well as guard against immune dysregulation, such as occurs in allergy and autoimmunity. Even greater respect for this powerful homeostatic system has emerged over the past few years with the increasing appreciation that immune cells also affect important non-immune functions, including neurodegeneration, cardiovascular function and metabolism. This Focus issue of *Nature Reviews Immunology*, produced with support from Sanofi-aventis, draws attention to an emerging frontier, immunometabolism, the interplay between immunological and metabolic processes. On the one hand, it has emerged that certain supposedly non-immune pathologies result in mobilization of the innate and adaptive immune systems, which, in the case of obesity, promotes metabolic abnormalities, culminating in increased susceptibility to type 2 diabetes, cardiovascular diseases, cancer and neurodegeneration. On the other hand, it is now clear that the behaviour of leukocytes and lymphocytes on many levels is controlled by internal metabolic properties. Dissection of the molecular underpinnings of immunological/metabolic cross-talk has become a priority.

Obesity and chronic disease

The obesity epidemic continues unabated in Western countries, and is rising even more dramatically throughout the rest of the world, paradoxically even in countries where poverty and malnutrition are most widespread. Coinciding with recent rises in obesity have been

proportional increases in medical conditions with obvious metabolic connections, such as cardiovascular disease, type 2 diabetes, fatty liver disease and cirrhosis. Additional associations are being drawn between obesity and diseases that are less obviously linked to metabolic derangements, including several forms of cancer, Alzheimer's disease and asthma. Inflammation has been aetiologically linked to the pathogenesis of each of these conditions, and as obesity is causally linked to a systemic low-grade subacute inflammatory state, as well as inflammation in adipose tissue, obesity-induced inflammation may be a common pathogenic denominator.

Two articles in this Focus issue discuss the relationship between adipose tissue expansion and inflammation. The article by Ouchi *et al*. focuses on adipokines, which are bioactive proteins produced by adipose tissue and have hormonal or cytokine actions locally and in other tissues. The article by Donath and Shoelson discusses the immunological effects of expanding fat mass and inflammation in insulin resistance and the effects of inflammation in pancreatic islets as these relate to the development and severity of type 2 diabetes.

Adipokines

Some adipokines, such as leptin and adiponectin, are produced exclusively (at least predominantly) in adipose tissue, whereas other so-called adipokines are more typical pro-inflammatory or anti-inflammatory cytokines that are best known for their roles in innate and adaptive immunity. The list of pro-inflammatory adipokines produced in fat tissues includes tumour necrosis factor (TNF), interleukin-6 (IL-6), resistin, retinol-binding protein 4 (RBP4) and the closely related protein lipocalin 2, CC-chemokine ligand 2 (CCL2), IL-18, nicotinamide phosphoribosyltransferase (NAMPT; also known as visfatin) and CXC-chemokine ligand 5 (CXCL5). The production of each of these adipokines is increased with adipose tissue expansion, suggesting that this contributes to the pro-inflammatory state associated with obesity and potentially to the deleterious consequences of obesity that are mediated by chronic inflammation. By contrast, anti-inflammatory adipokines and other cytokines produced in fat, including adiponectin, IL-10[1] and the WNT inhibitor soluble frizzled-related protein 5 (SFRP5)[2], seem to decrease with fat mass expansion, and this could also contribute to the pro-inflammatory state associated with obesity and its deleterious consequences. Although all of the adipokines are found in adipose tissue, the relative amounts produced by adipocytes versus macrophages, endothelial cells, T cells and mast cells, for example, are in many cases unknown. Also unknown are the relative contributions of the adipokines as primary inhibitors of insulin sensitivity and secretion versus their effects on leukocyte recruitment and activation, with associated effects on insulin resistance and secretion.

Inflammation and anti-inflammatory strategies in type 2 diabetes

Attempts to target inflammation in type 2 diabetes have moved quickly for two main reasons. Foremost is the robustness of the clinical endpoint, that is, changes in measures of glycaemic control. Fasting blood glucose and haemoglobin A1c levels are easily measured and highly accurate and reproducible. Fasting blood glucose changes within days to weeks of initiating a therapy, whereas haemoglobin A1c levels provide an 8–12 week integrated

average blood glucose measure. It is therefore possible to test the efficacy of anti-inflammatory strategies within weeks for initial assessment and in months for highly predictive results. This is in contrast to assessments of drug efficacy and safety in other conditions such as cardiovascular disease, which requires much larger trial size and duration – hence much greater cost – to assess true clinical outcomes. Trials of drugs to prevent Alzheimer's disease are even more challenging, as the common forms of the disease cannot be predicted prior to disease onset, which makes trial size and duration, and costs, prohibitive. Clinical trials that assess effects on biomarkers that associate with cardiovascular disease or Alzheimer's disease can be smaller and of shorter duration, but their ability to predict clinical outcomes is often weak or unknown. As trials in type 2 diabetes can be conducted using reasonable numbers of subjects and at a reasonable cost, they may be used as a screen for potential anti-inflammatory treatments for other obesity-induced chronic diseases that are more difficult to study.

Completed and ongoing trials are testing this possibility. Three strategies discussed by Donath and Shoelson are the use of salicylates, such as salsalate, and neutralization of either IL-1 or TNF. Small clinical trials report positive outcomes following selective blockade of IL-1 receptor 1, either with specific antibodies or recombinant IL-1 receptor antagonist[3,4]. Salsalate is a prodrug form of salicylate (an orally active, small molecule anti-inflammatory drug) and has also been shown to lower blood glucose levels in patients with type 2 diabetes [5–7]. IL-1 antagonism and salsalate are both being tested further in larger clinical trials. While small clinical trials using TNF blockade have not provided improvements in blood glucose levels in patients with type 2 diabetes, encouraging results in non-diabetic patients being treated with TNF blockers for other conditions suggest that this might be worth re-exploring.

Unique uses of metabolic pathways in immune cells

A completely different perspective on the immunological/metabolic interface is the extent to which, and the precise mechanisms by which, typical cell-intrinsic metabolic processes influence the performance of immune cells. In most cases, immune cells use and respond to nutrients similarly to other cells, so it is the exceptions to the rules that may be most interesting. The serine/threonine kinases AKT, AMPK (AMP-activated protein kinase), mTOR (mammalian target of rapamycin) and LKB1 are generally thought of as cellular nutrient sensors that help to maintain energy homeostasis by relaying signals that determine how cells respond to high or low levels of intracellular carbohydrate or amino acids. Finlay and Cantrell suggest that in addition to their more established roles in nutrient responses, AKT, AMPK and LKB1 control a fate switch, from cytotoxic effector to memory $CD8^+$ T cells. They argue that in $CD8^+$ T cells the main role for AKT is to regulate repertoires of adhesion molecules and chemokine receptors and hence to control trafficking and migration, and that this is what determines memory versus terminally differentiated effector T cells.

A separate series of investigations looked are the effects of LKB1 in haematopoietic stem cells (HSCs)[8–10]. As noted above, in most cells LKB1 is a serine/threonine kinase that is upstream of AMPK (a master regulator of energy homeostasis) and the mTOR complex (a protein complex that controls protein synthesis and cell proliferation). These three reports

show that LKB1 regulates the function and dynamics of HSCs through pathways that are independent of AMPK and the mTOR complex. Deletion of *Lkb1* in mice lead to an initial expansion of HSCs and multipotent progenitors, but over time the cells were depleted and mice became pan-cytopaenic. Moreover, a $Lkb1^{-/-}$ bone marrow transplant was unable to reconstitute the haematopoietic system in irradiated mice, again suggesting that the survival of HSCs depends on LKB1. These latter two examples show that under certain conditions, immune cells may use metabolic pathways to control fate and function in different ways than other cells.

Thus, the emerging field of immunometabolism has already yielded some novel insights, which have theoretical and practical implications for future work. On the theoretical side, several important questions have been raised, notably: To what extent are obesity and inflammation triggered in parallel or in sequence? If primarily the former, what is the common initiating signal? If essentially the latter, what signals link the two processes? Why does obesity-associated inflammation persist, as opposed to being held in check? By what pathway(s) does inflammation provoke type 2 diabetes, cardiovascular disease and other downstream pathologies? Can genetic and environmental factors reinforce or dissociate the link between metabolic and immunologic abnormalities? Practically, the finding that inflammation mediates many of the pathologic consequences of obesity raises the hope of exploiting the existing armamentarium of ant-inflammatory drugs, or future ones, to treat patients with obesity-associated metabolic and cardiovascular disorders (and even perhaps some cancers and neurodegenerative diseases). Underscoring this potential, the diabetes drug metformin has shown promise in cancer prevention[11], and is being tested in trials to prevent a variety of cancers. And even more to the point, once daily aspirin (an anti-inflammatory salicylate) use correlates with reduced death from several different cancers[12].

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