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Immune Regulators of Inflammation in Obesity-Associated Type 2 Diabetes and Coronary Artery Disease

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Abstract

Purpose—To summarize current work identifying inflammatory components that underlie associations between obesity-associated type 2 diabetes (T2D) and coronary artery disease (CAD).

Recent findings—Recent studies implicate immune cells as drivers of pathogenic inflammation in human T2D. Inflammatory lymphocytes characterize unhealthy adipose tissue (AT), but regional adipose volume, primarily visceral and pericardial fat; also predict severity and risk for obesity-associated CAD. Having a greater understanding of shared characteristics between inflammatory cells from different AT depots and a more accessible tissue such as blood will facilitate progress towards clinical translation of our appreciation of obesity as an inflammatory disease.

Summary—Obesity predisposes inflammation and metabolic dysfunction through multiple mechanisms, but these mechanisms remain understudied in humans. Studies of obese subjects have identified disproportionate impacts of specific T cell subsets in metabolic diseases like T2D. Based on demonstration that AT inflammation is depot-specific, analysis of adiposity by waist-to-hip ratio or magnetic resonance imaging (MRI) will increase interpretive value of lymphocyte-focused studies and aid clinicians in determining which obese individuals are at highest risk for CAD. New tools to combat obesity-associated CAD and other co-morbidities will stem from identification of immune cell-mediated inflammatory networks that are amenable to pharmacological interventions.

Keywords

coronary artery disease; obesity; inflammation; T cell; B cells; type 2 diabetes

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Disclosure

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Introduction

The prevalence of obesity continues to increase worldwide and with current trajectories obesity will burden healthcare systems for decades [1*]. Obesity often triggers the inflammation that is believed to increase risk for many co-morbidities, with greatest risk stemming from the simmering inflammation that underlies type 2 diabetes (T2D) and coronary artery disease (CAD)[2**, 3]. Obesity-associated inflammation is largely due to overproduction of pro-inflammatory cytokines by macrophages [4, 5], B cells and T cells [6–10**], all of which are recruited to expanding AT. Immune cell-mediated inflammation reinforces a pro-inflammatory balance of adipokines, or adipocyte cytokines, which are also increased in expanding AT [11]. This combination of cytokines from adipose-associated immune cells plus adipokines promotes metabolic dysregulation that includes insulin resistance (IR) and T2D [12*, 13]. The pro-inflammatory cytokine profile in obesity likely spills over into the circulation, where increased serum cytokines predict increased CAD risk [14, 15], pulmonary diseases [16–18] and cancer [19]. Inflammation may thereby link seemingly disparate co-morbidities of obesity.

Although mouse models have enabled substantial progress over the last decade in describing immune compartment contributions to metabolic dysfunction, an understanding of the role inflammation plays in human obesity and associated metabolic disease remains rudimentary. Recent findings from human studies reviewed herein highlight ongoing progress in our understanding of inflammation as a driver of obesity-associated disease with emphasis on CAD.

Obesity-associated inflammation and immune cells in T2D

A major advance in metabolic research came with the understanding of obesity as a chronic, low-grade inflammatory state, which differs from the immune response to infection but involves well-understood modulators of nutrient storage and efflux pathways [8, 20, 21*]. It was observations that activated macrophages within AT produce the majority of adipose-associated pro-inflammatory cytokines, and that these cytokines promote IR [4, 5] which provoked the current focus on multiple types of immune cells in metabolic research and founded the field of “Immunometabolism”. Extensive genetic, dietary and pharmacologic interventions in mouse models in parallel with observations from human studies identified a causal link between obesity-associated inflammation and metabolic disease [22, 23]. Such studies also revealed a role for macrophages in tissue remodeling within AT of lean individuals that contrasts with pro-inflammatory functions of newly recruited and/or *in situ* proliferating macrophages of obese AT [24*]. Other myeloid immune cells including neutrophils, eosinophils and mast cells also play roles in promoting inflammatory responses and IR in obese AT [25–27].

Classically designated “adaptive” immune cells, including B cells, CD8⁺ and CD4⁺ T cells, also infiltrate AT and increase in number in response to obesity [28*, 29] (Figure 1). Both B and T cells release and/or stimulate release of pro-inflammatory cytokines in obesity-associated IR/T2D, bolstering local and systemic inflammation. In addition to the B cell-intrinsic changes in T2D humans and obese/IR mice, B cells stimulate inflammatory

cytokine production by CD4⁺ and CD8⁺ T cells [6, 10]. Thus B cells promote T2D-associated inflammation through direct (cell-intrinsic) and indirect (T cell-mediated) mechanisms. Further work with human samples showed that contact between B and T cells is required for maximal pro-inflammatory CD4⁺ Th17 cell function in samples from T2D but not from obese, non-diabetic subjects. Although anti-inflammatory functions of B cells and regulatory T cells (Tregs) have also been well-defined, these functions appear to be diminished in obesity [8, 30–32]. For example, B cells from lean, ‘metabolically healthy’ humans and mice release significant amounts of the anti-inflammatory cytokine IL-10, but B cell IL-10 is severely down-regulated in response to obesity/IR/T2D [10, 33]. This shift to a potentially pathogenic, pro-inflammatory B cell cytokine profile may mechanistically underlie demonstrations that B cell-null mice fed a high-fat diet (HFD) are equally obese but less prone to obesity-associated IR and other metabolic disturbances. Anti-inflammatory CD4⁺ T regulatory cells (Tregs) are similarly underrepresented in obese/IR mice and T2D humans, in part due to lower numbers of Tregs [8, 34] but also likely due to suppression of anti-inflammatory IL-10 production [35*], although clarification is needed in follow-up studies with human samples. Despite overall similarities in roles for B and T cells in human and mouse T2D, a more comprehensive assessment of T cells in obesity suggests fundamental differences in obesity-associated inflammation between humans and mice, obese mice have predominantly CD8 and Th1 inflammatory responses with minor changes in Th17 cells [8, 9], whereas in obese humans the Th17 axis dominates T cell-mediated inflammation [10, 33, 36, 37**].

Th17, in obesity and T2D

The importance of T cell cytokines such as IFN γ and IL-17 in obesity is less appreciated than thoroughly examined, classical “diabetogenic” cytokines (e.g., TNF- α , IL-6 and IL-1 β) [22]. Th17 cells, the dominant source of IL-17, are instead recognized primarily for roles in clearance of select pathogens, and for detrimental effects in autoimmune diseases such as multiple sclerosis (mouse EAE) [38* 39]. Data showing that IL-6 and IL-1 β drive Th17 differentiation [40, 41*] is part of an emerging appreciation of Th17 expansion in obesity-associated IR/T2D. Recently, leptin, an adipokine generally increased in obesity/IR, was shown to also support Th17 expansion [42*, 43]. Overall, the relationship between increased IL-6/IL-1 β /leptin and increased Th17 differentiation, coupled with the importance of Th17s in autoimmune diseases, may explain clinical evidence that obesity predisposes people to increased risk for inflammation-mediated autoimmune diseases including psoriasis, rheumatoid arthritis [44], lupus [45] and multiple sclerosis [7, 46].

Despite these likely mechanistic links between obesity-associated inflammation and Th17 cells, the Th17 signature cytokines IL-17 and IL-22 have been more or less dismissed in mouse models of obesity and T2D, in part because IL-17⁺ cells (likely Th17s) infiltrate murine subcutaneous rather than visceral AT in response to HFD [47], or Th17s dominate only after obesity/IR is established [48]. IL-17 gene deletion caused an abnormal weight gain on both low-fat (LF) or HFD compared to WT controls, precluding a straight-forward interpretation of roles for Th17 cells in obese knockout animals [49]. This lack of strong data for IL-17/Th17 dominance in obesity-associated IR in mice has moderated excitement over possible functions of Th17s in human obesity/IR/T2D, although several reports have

shown IL-17 and IL-22 induced IR in chief metabolic regulators such as hepatocytes, adipocytes and myocytes [37, 49, 50].

Evidence of a role for Th17s in human disease includes demonstrations that plasma Th17 cytokines and *in vitro* Th17 activity tightly correlate with measures of glycated hemoglobin A1c levels of T2D patients [33, 36, 51*]. Two recent studies also showed increased Th17 function (i.e. IL-17 and IL-22 production) AT-associated immune cells from well-characterized obese/insulin sensitive (IS) versus obese/IR subjects [37, 52**]. Taken together, this work suggested some aspects of human immunometabolism should be more thoughtfully examined with animal models that more closely recapitulate human physiology. One example of such an approach is long term (9 month) HFD feeding of genetically homogeneous C57BL6 mice, which surprisingly revealed 4 different metabolic response groups. These groups include the lean/IR and obese/IS groups that are generally absent (or even culled) following standard 12–16 wk feeding protocols [53]. Measuring cytokines from these metabolic groups of mice or investigation of strains of mice with resistance to diet-induced obesity [54] could facilitate progress in understanding mechanisms underlying immune cell/cytokine involvement in patients.

Obesity, inflammation and associated coronary artery disease (CAD)

Western diet together with obesity, T2D, hypertension, dyslipidemia, physical inactivity, and increasing average age, are believed to be primary causes of CAD and CAD-associated heart failure, the leading cause of death in T2D individuals [55]. The role of inflammation in CAD has been appreciated for decades, with a relatively early appreciation that local immune cell infiltrates characterize CAD and can specifically predict risk for fatal outcome [56, 57]. Immune cell infiltrates occur downstream of endothelial dysfunction, which promotes lipoprotein transcytosis from the plasma into the vessel intima. Subsequent immune cell infiltration/activation thereby links endothelial changes to cardiovascular disease/CAD (Reviewed in [58, 59]. Teasing out the complex interactions amongst obesity, CAD and T2D is a daunting endeavor, but the appreciation of inflammation as a critical mediator primes the field to expand the findings above thus spur fundamentally new clinical approaches.

Documented roles for macrophages, T cells and B cells in CAD suggest that obesity-associated inflammation bridges immune cell function and CAD [60–66]. Macrophages were the first immune cell recognized to play critical roles in the development of atherosclerosis, from early fatty streak formation through progression to vulnerable plaques. Mechanisms of macrophage involvement in CAD include the ability to form foam cells, and to secrete high amounts of pro-inflammatory, pro-CAD cytokines such as TNF α , IL-1 β , IL-6 and IL-8 [60, 67–72].

Pro-inflammatory T cells also play critical roles in the endothelial dysfunction that precedes CAD [61–65]. IFN γ , a pro-inflammatory cytokine produced by both CD4⁺ and CD8⁺ T cells, is critical for the development of atherosclerosis. Furthermore, inhibition of Th1 cells, thus IFN γ and other CD4⁺-associated cytokines, ameliorates disease in mouse models (Reviewed in [73], independently indicating Th1s promote CAD. Similarly, IL-17, the major

cytokine produced by Th17s, is important for the recruitment of macrophages to developing atherosclerotic lesions [61, 74, 75*], and both CD4⁺ and CD8⁺ T cells characterize unstable plaques (71–74). Thus, multiple lines of evidence suggest that pro-inflammatory T cells support obesity-associated atherosclerosis and may link CAD to T2D.

B cells are more recently appreciated mediators of CAD, although their roles are more complex than the pro-atherogenic functions of macrophages and T cells. B cell depletion protects against CAD in model animals [66], suggesting B cells are pathogenic. In contrast, some studies show that B cells protect against atherosclerosis [76]. The latter interpretation is consistent with the demonstration that removal of the normal splenic reservoir of B cells renders patients more susceptible to CAD [77]. Although exact mechanisms are not known, these seemingly contradictory findings on roles for B cells in atherosclerosis may be explained by demonstrations that B cells can initially protect against inflammatory disease, but then can change their activity, promoting pathogenesis [10, 34, 78]. For example, the loss of B cell IL-10 in T2D discussed above, coupled with a T2D-associated increase in the ability of B cells to produce CAD-associated IL-8 [72, 79] is consistent with a disease-associated gain of pathogenic B cell function. B cells also promote pericardial AT expansion and inflammation in a mouse model of obesity-associated IR [10, 34]. Taken together, these reports suggest that B cells from obese/IR subjects support CAD-associated inflammation through multiple mechanisms such as 1. promoting pro-inflammatory cytokine production including high IL-8 and low IL-10 release [34, 69, 80, 81], 2. by supporting AT expansion in obesity [10], and 3. promoting pro-inflammatory Th17 cells [6, 10, 82]. Both the activities of individual immune cells and the cross-talk amongst immune cell subsets raise the clinically critical possibility that immunomodulatory drugs, such as the generally safe B cell depletion drug rituximab [83, 84] may have unappreciated efficacy in the prevention of obesity-associated CAD [85].

The role of pericardial AT (pAT) in local inflammation and CAD

Although adipose depots all increase in volume with obesity, fat deposits in different anatomical regions show depot-associated levels of immune cell infiltration and inflammation, and thus differentially associate with disease. To generalize, subcutaneous AT is more metabolically “protective”, while pericardial and other visceral depots are highly correlated with risk for obesity-associated disease, including CAD [86–88]. The recognition that pAT physiology, which includes pAT inflammation, is a critical mediator of CAD significantly departs from the outdated assumption that pAT expansion is an uninteresting epiphenomenon of both obesity-independent and obesity-associated CAD.

Numerous analyses point to the importance of pAT expansion and concomitant inflammation in obesity/IR-associated CAD. pAT from subjects with CAD has increased inflammatory hallmarks compared to pAT from subjects undergoing non-CAD heart procedures [72, 89–91]. Notably, pAT volume also associates with systemic inflammation, as measured by IL-6 and C-reactive protein (CRP) levels [92]. Also, CAD is more tightly associated with the amount of pAT in lean individuals than with a variety of more “accepted” CAD risk factors, including body fat distribution [93]. pAT volume is a strong independent risk factor for CAD severity [88], and positively associates with calcified

coronary plaque [94, 95] which suggests that pAT may exert local toxic effects on the coronary vasculature [96]. Thus it is unsurprising that the amount of pAT negatively correlates with cardiac output and stroke volume [97]. Additionally, epidemiological studies show that relatively high pAT volume ($>300\text{cm}^3$) associates with a 4-fold increased risk of CAD, whereas smoking and T2D increase CAD risk 1.6- and 3-fold, respectively [98]. Prospective studies revealed that the volume of epicardial AT, the depot that literally coats the myocardium, is predictive of obstructive CAD even before patients develop overt pathology [99*–101]. Finally, perhaps the most convincing human evidence linking obesity, inflammation and CAD is analysis of monozygotic twins discordant for obesity. This study found that the obese twin had a greater epicardial AT volume, and that CRP, one surrogate for systemic inflammation, was the only one of several factors measured that significantly associated with epicardial AT volume. These studies support the conclusion that inflammation and epicardial AT volume predict risk for CAD [102*, 103] and highlight the urgency of a more comprehensive analysis of pAT physiology focused on inflammation, to advance the long-term goal of countering CAD pathogenesis.

Together the associations between pAT inflammation and CAD/impaired cardiovascular function, plus the known roles of obesity in AT volume and pro-inflammatory immune cell function [4–7, 10, 33, 34, 47, 72, 79, 89, 91, 104] frame the idea that obesity-associated changes in pAT physiology link obesity and CAD, and are further exacerbated in the presence of IR. However, one gap in the pAT analyses is that “pAT” is often imprecisely defined, and can denote the epicardial AT that coats the heart, the interstitial AT that coats the outside of the pericardial membrane (thus does not directly touch the heart) or both. Both heart-proximal depots (Figure 2) are linked to local and systemic inflammation, although each is also somewhat distinct from the other [72, 89–92, 105, 106*]. Epicardial AT may disproportionately impact CAD due to a shared circulation with the myocardium [107]. Regardless, a comparison of physiology of epicardial fat, interstitial fat and blood from the same individual is essential to comprehensively understand inflammation in heart-proximal AT, and will be vital for identifying pAT signatures in a more accessible tissue.

A clinically important, yet unappreciated aspect of studies on obesity, inflammation and CAD is the possibility that fundamentally different mechanisms drive CAD in lean/IS compared to obese/IS or obese/IR subjects. This novel prospect is raised by our recent work showing mechanisms of periodontitis (PD), another common comorbidity in obesity/IR, significantly differ between lean/IS and obese/IR mice [108]. Lean mice developed PD through a B cell-independent process, while PD development in obese/IR mice was highly B cell-dependent. Obesity-associated inflammatory responses in PD and CAD are inadequately studied in humans, although one cross-sectional study of obese subjects with and without PD identified that both obesity and PD increased risk for cardiovascular disease [109*]. Future identification of correlates of CAD over a range of metabolic status with subsequent mechanistic analyses will be needed to determine whether the currently similar standard of care for CAD in lean and obese/IR patients is the best approach.

Conclusion

Our developing appreciation of links among obesity, inflammation and CAD will require multiple complementary approaches to leverage new concepts into translatable outcomes. Careful characterization of human subjects, particularly analysis of AT distribution by measures as simple as waist: hip ratio, will be needed to stratify subjects that are most likely obese/metabolically healthy from those that are obese/metabolically unhealthy [93, 110]. Notably, subjects with T2D are most effectively analyzed as a unique cohort, rather than being lumped into the “obese/IR” category. Use of models that more closely parallel human disease will increase the translational significance of studies. A call for simple analysis of metabolic status in all clinical drug trials (for example, HbA1c) would identify drugs with potential efficacy against obesity-associated CAD, while incurring minimal extra cost. Similarly, collection of (at least) serum and peripheral blood mononuclear cells from all obesity or CAD-associated clinical trials would provide samples for testing of new possibilities, like Th17 dominance. Concepts developed in human sample studies, with further testing in models to refine concepts, will integrate the strengths of both bench and bedside research to allow the field to exploit our understanding of obesity-associated inflammation for clinical gains over the short term.

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Key points

1. Obese AT causes a shift towards pro-inflammatory Th17 immune response in humans, which differs from the Th1/CD8+ T cell dominance of murine obesity/insulin resistance.
2. Pro-inflammatory T cell responses may underlie increased risk for obesity associated CAD.
3. Classifying subjects within obese cohorts such as by depot-specific immune responses or specific adipose depot volume will assist in developing criteria for obesity-associated inflammation, CAD risk and severity.

Figure 1.

Role for immune cells in inflammatory response of metabolically healthy obese (insulin sensitive) and metabolically unhealthy (insulin resistant) obese adipose tissue. Blue= IL-10^{hi} B cell, Light blue= IL-10^{lo} B cell, Orange= Th1 cell, Dark Green=Th17 cell, Yellow=regulatory T cells (Tregs) Purple oval= anti-inflammatory M2 macrophages (M2 ϕ), pink oval=pro-inflammatory M1 macrophage (M ϕ). Anti-inflammatory immune cells dominate metabolically healthy tissue, but decrease in metabolically unhealthy tissue. In contrast, pro-inflammatory immune cells dominate metabolically unhealthy tissue. Original artwork.

Figure 2.

Depiction of regional adipose tissue (AT) deposition in human body and obesity-associated gene and cytokine profiles. AT depots that preferentially expand in metabolically unhealthy (inflammatory) responses include pericardial (epicardial and interstitial) and visceral depots. AT that preferentially expands in metabolically healthy obese individuals includes widespread subcutaneous depots. Shown are up- or down-regulated genes, adipokines, or cytokines associated with obesity comorbidities, T2D and CAD. Original artwork.