Published in final edited form as:
J Investig Med. 2012 December ; 60(8): 1147–1150. doi:10.231/JIM.0b013e318271fdb9.

How does high fat diet induce adipose tissue fibrosis?

Hyokjoon Kwon and **Jeffrey E. Pessin**
Departments of Medicine and Molecular Pharmacology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461

Inflammation and Insulin resistance

Obesity is the single pre-disposing factor for Type 2 diabetes mellitus (T2DM) and is a major contributor to a variety of health issues including liver and cardiovascular diseases. In parallel, T2DM is a quickly growing global metabolic disease characterized by impaired insulin secretion and insulin resistance (1). Recent evidence has indicated that inflammation is one important contributing process for the development of insulin resistance in obese humans and rodents, and adipose tissue has been shown as a major site mediating the inflammatory response (2–4). White adipose tissue consists of a variety of cell types including adipocytes, macrophages, lymphocytes, pre-adipocytes, and endothelial cells. Innate immune response mainly mediated by macrophages is a key inflammatory process in adipose tissue resulting in insulin resistance. Macrophages differentiate into two generally functional distinct populations, although there are numerous macrophage subtypes that appear to represent a continuum and interconversion with discrete functions. In a simplified version, the classically activated macrophages (M1, pro-inflammatory) induced by Th1 cytokines such as IFN-γ express nitric-oxide synthase (NOS2) whereas the alternatively activated macrophages (M2, anti-inflammatory) induced by Th2 cytokines such as IL-4 and IL-13 express arginase-1 (ARG1) (5–9). $F4/80^{+}CD11c^{+}$ inflammatory M1 macrophages are increased in adipose tissue and secrete inflammatory cytokines such as tumor necrosis factor-α (TNF-α), Interleukin-6 (IL-6) and IL-1β. TNF-α levels are increased obese diabetic humans and rodents, and neutralization of TNF-α improves insulin sensitivity in obese rodents (10). TNF-α induces serine phosphorylation of IRS1 to inhibit signaling to downstream effectors of the insulin receptor resulting in insulin resistance (11). IL-1β is also elevated in circulation (12) and in pancreatic islets of obese T2DM humans and rodents and induces the loss of pancreatic β cell mass resulting in hyperglycemia (13–15). IL-1β is mainly produced by monocytes and macrophages being synthesized as a IL-1β precursor in the cytosol, and activation-induced NALP3 (cryopyrin) inflammasome activates caspase-1 to mediate active IL-1β secretion (16). IL-1β binds to IL-1 receptor Type I (IL-1RI) and IL-1 receptor accessory protein (17) and recruits MYD88, IRAK4, and TRAF6 to activate NF-κB and MAPKs.

Recently, adaptive immune responses have been shown to be a critical factor for high fat diet (HFD)-induced inflammation and insulin resistance in humans and rodents (Figure 1). $Foxp3^{+}CD4^{+}$ regulatory T (Treg) cells (anti-inflammatory IL-10 producing cells), IL-4 producing Th2 $CD4^{+}$ T cells, and eosinophils are decreased whereas effector $CD8^{+}$ T cells, IFN-γ producing Th1 $CD4^{+}$ T cells, and autoantibody producing B cells are increased in obese mice (18–21). Interestingly, adoptive transfer of $CD4^{+}$ cells, which produce IL-4 and IL-13, rescues HFD-induced obesity and insulin resistance in *Rag1* deficient mice (18)

Please address correspondences to: Dr. Hyokjoon Kwon, Departments of Medicine and Molecular Pharmacology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, USA, Tel: 718-678-1031, Fax: 718-678-1020, hyok.kwon@einstein.yu.edu.

suggesting that Th2 cytokines such as IL-4 and IL-13 suppress HFD-induced inflammation to improve insulin sensitivity. In addition, IL-13 and IL-4 mediate Th2 immune responses to activate eosinophils, basophils, and B cells resulting in the clearance of extracellular parasites (6). IL-13 is a four-helix bundle short-chain and Th2 $CD4^+$ T cell-derived cytokine that is also involved in allergic inflammation, asthma, tissue remodeling, and in this context fibrosis (22, 23). IL-13 is a ligand for IL-13Rα1 and IL-13Rα2 receptors (24–27). IL-13Rα1 is a low affinity receptor by itself, but forms a high affinity receptor with IL-4Rα to generate an IL-4Rα and IL-13Rα1 heterodimer, termed the Type II IL-4 receptor (IL-4RII) (28, 29). As IL-4RII shares IL-4Rα and IL-13Rα1, IL-13 activates JAK1, Tyk2, and STAT6, and although IL-13 and IL-4 are functionally related, conventional IL-13 deficient mice demonstrate a unique role of IL-13 in Th2 immune responses (30).

Immune responses in tissue fibrosis

Fibrosis is a common pathological consequence of many inflammatory diseases such as idiopathic pulmonary fibrosis, liver cirrhosis, systemic sclerosis, and progressive kidney disease (22, 23). Therefore, fibrotic disorders are a critical problem of morbidity and mortality worldwide and cause about 45% of deaths in the United States (31). Intensive studies to understand the molecular mechanisms of fibrosis have shown that IL-13 and transforming growth factor-β1 (TGF-β1) are key regulators (32–35), and activated fibroblasts produce extracellular matrix (ECM) including collagens, elastins, and proteoglycans (22, 31) resulting in the pathogenesis of fibrosis. Damaged epithelial and endothelial cells secrete inflammatory mediators to initiate blood clotting and epithelial/endothelial cells and platelets produce chemokines and growth factors such as TGF-β and PDGFs to recruit neutrophils and macrophages. Furthermore, T cells, B cells and eosinophils are recruited to generate pro-fibrotic cytokines such as IL-13 and TGF-β1. Fibroblasts are also accumulated in injured region from epithelial-mesenchymal transition (EMT) and bone marrow derived fibrocytes. Fibroblasts are activated by IL-13 and TGF-β1 and then differentiate into α-smooth muscle actin (SMA) expressing myofibroblasts to produce ECM. Myofibroblasts, macrophages and epithelial/endothelial cells also produce matrix metalloproteinases (MMP) and tissue inhibitors of matrix metalloproteinases (TIMP) for ECM regulation. Therefore, the balance between ECM formation and degradation is a critical process for normal tissue repair. Tissue repair process becomes pathogenic fibrosis if the balance between ECM formation and degradation is not tightly regulated resulting in the distortion of normal tissue architecture and function.

Fibrosis is closely linked with Th2 immune responses, and especially IL-13 produced by Th2 $CD4^+$ T cells is the major cytokine to mediate tissue fibrosis (31, 36, 37). The expression of IL-13 is increased in tissues and bronchoalveolar lavage (BAL) fluid in idiopathic pulmonary fibrosis (IPF), sarcoidosis and liver fibrosis. However molecular mechanisms to mediate IL-13-induced tissue fibrosis are complicated. The pro-fibrotic effects of IL-13 are dependent on TGF-β1 in lung fibrosis (34, 35). Three isotypes of TGF-β (TGF-β1, -β2 and β3) have been found in mammals, and TGF-β1 mainly produced by monocytes and macrophages is the major isotype to mediate tissue fibrosis. IL-13 induces MMP-9 and activates cathepsin-based proteolytic pathways to cleave latency-associated protein (LAP) for the generation of active TGF-β1 resulting in the stimulation of myofibroblasts to produce ECM. In contrast, IL-13-induced liver fibrosis in schistosomiasis is TGF-β1 independent (38). *S. mansoni* infected IL-13 deficient mice showed improved liver fibrosis although TGF-β production is not diminished. Furthermore, the treatment of neutralizing TGF-β antibody, TGF-βR-Fc, and Smad3 deficient mice do not modulate development of liver fibrosis and production of IL-13 in schistosomiasis suggesting that *S. mansoni* induced liver fibrosis is mediated by IL-13 but TGF-β1 independent. Therefore, IL-13 and TGF-β1 appear to be critical cytokines mediating tissue fibrosis. However, the

specific pathways and mechanisms dictating the independent and cooperative interaction of IL-13 and TGF-β1 in the pathogenesis of specific tissue fibrosis remain enigmatic.

Unique microenvironment in adipose tissue fibrosis

Adipose tissue stores excess nutrition and also releases fatty acids to compensate nutrition deprivation. Thus adipose tissue maintains whole body energy homeostasis through hyperplasia and hypertrophy. Excess nutrition initiates adipocytes expansion along with triglyceride accumulation, adipocytes cell death, adipokine/cytokine production, endoplasmic reticulum stress and adipose tissue hypoxia resulting in the immune cell infiltration, low grade chronic inflammation and adipose tissue fibrosis in both humans and rodents (3, 39–43). Collagen type VI is a dominant ECM in mice and collagen VI deficient ob/ob and HFD fed mice have reduced adipose tissue fibrosis with improved insulin sensitivity suggesting that adipose tissue fibrosis may be an important determinant of insulin sensitivity (41). Adipocytes hypertrophy induces the expression of hypoxia-inducible factor 1α (HIF-1α), and increased lysyl oxidase one of target genes of HIF-1α mediates cross linking of collagens for adipose tissue fibrosis (42). In parallel, obesity in humans is recently shown to be associated with adipose tissue fibrosis. White adipose tissues of obese humans have more collagen deposition than lean subjects (40). Adipose tissue fibrosis may induce rigid extracellular environment, which restrains adipocyte expansion and then triggers adipocyte cell death and inflammatory responses by increased mechanical stress.

Obese humans and rodents show accumulated diverse inflammatory immune cells in adipose tissue (18–21), and interactions between macrophages and pre-adipocytes are involved in ECM production (43) suggesting that immune cells such as macrophages and T cells are involved in adipose tissue fibrosis. However molecular mechanisms of HFD-induced adipose tissue fibrosis is not clear. IL-13 is the critical mediator in liver and lung fibrosis, and Th2 $CD4^+$ T cells are major source of IL-13 to produce ECM. However, the expression of IL-4 is significantly diminished (21) whereas IL-13 levels are increased in adipose tissue of HFD-induced obese rodents (unpublished results). Since Th2 $CD4^+$ T cells and eosinophils are decreased after HFD feeding, it is likely that non-$CD4^+$ T cells are responsible for the production of IL-13 in adipose tissue (Figure 2). In addition, IFN-γ produced by Th1 $CD4^+$ T cells suppresses the differentiation of alternatively activated M2 macrophages and Th2 $CD4^+$ T cells resulting in the abrogation of tissue fibrosis in the liver (44, 45). In contrast, IFN-γ producing $CD4^+$ T cells are increased in adipose tissue of HFD fed or genetically modified obese mice although adipose tissue fibrosis is enhanced. Thus in contrast to the liver, adipose tissue has unique molecular mechanisms driving fibrosis in vivo. We suggest that HFD induces the expression of IL-13 from non-Th2 $CD4^+$ T cells and may mediate the deposition of collagen to induced adipose tissue fibrosis even though IFN-γ expression is enhanced due to increased Th1 $CD4^+$ T cells. To elucidate molecular mechanisms of HFD induced adipose fibrosis, one important goal is to identify the source of IL-13 in adipose tissue and signaling pathway mediating the expression of IL-13 in adipose tissue.

References

1. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. JAMA. 2006; 295:1549–55. [PubMed: 16595758]
2. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006; 444:860–7. [PubMed: 17167474]
3. Schenk S, Saberi M, Olefsky JM. Insulin sensitivity: modulation by nutrients and inflammation. J Clin Invest. 2008; 118:2992–3002. [PubMed: 18769626]

4. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest. 2006; 116:1793–801. [PubMed: 16823477]

5. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol. 2004; 25:677–86. [PubMed: 15530839]

6. Martinez FO, Helming L, Gordon S. Alternative activation of macrophages: an immunologic functional perspective. Annu Rev Immunol. 2009; 27:451–83. [PubMed: 19105661]

7. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nat Rev Immunol. 2008; 8:958–69. [PubMed: 19029990]

8. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest. 2007; 117:175–84. [PubMed: 17200717]

9. Lumeng CN, Deyoung SM, Bodzin JL, Saltiel AR. Increased inflammatory properties of adipose tissue macrophages recruited during diet-induced obesity. Diabetes. 2007; 56:16–23. [PubMed: 17192460]

10. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993; 259:87–91. [PubMed: 7678183]

11. Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha-and obesity-induced insulin resistance. Science. 1996; 271:665–8. [PubMed: 8571133]

12. Spranger J, Kroke A, Mohlig M, Hoffmann K, Bergmann MM, Ristow M, Boeing H, Pfeiffer AF. Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Diabetes. 2003; 52:812–7. [PubMed: 12606524]

13. Donath MY, Gross DJ, Cerasi E, Kaiser N. Hyperglycemia-induced beta-cell apoptosis in pancreatic islets of Psammomys obesus during development of diabetes. Diabetes. 1999; 48:738–44. [PubMed: 10102689]

14. Ehses JA, Lacraz G, Giroix MH, Schmidlin F, Coulaud J, Kassis N, Irminger JC, Kergoat M, Portha B, Homo-Delarche F, Donath MY. IL-1 antagonism reduces hyperglycemia and tissue inflammation in the type 2 diabetic GK rat. Proc Natl Acad Sci U S A. 2009; 106:13998–4003. [PubMed: 19666548]

15. Sauter NS, Schulthess FT, Galasso R, Castellani LW, Maedler K. The antiinflammatory cytokine interleukin-1 receptor antagonist protects from high-fat diet-induced hyperglycemia. Endocrinology. 2008; 149:2208–18. [PubMed: 18239070]

16. Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. Annu Rev Immunol. 2009; 27:519–50. [PubMed: 19302047]

17. Sims JE, Smith DE. The IL-1 family: regulators of immunity. Nat Rev Immunol. 2010; 10:89–102. [PubMed: 20081871]

18. Winer S, Chan Y, Paltser G, Truong D, Tsui H, Bahrami J, Dorfman R, Wang Y, Zielenski J, Mastronardi F, Maezawa Y, Drucker DJ, Engleman E, Winer D, Dosch HM. Normalization of obesity-associated insulin resistance through immunotherapy. Nat Med. 2009; 15:921–9. [PubMed: 19633657]

19. Nishimura S, Manabe I, Nagasaki M, Eto K, Yamashita H, Ohsugi M, Otsu M, Hara K, Ueki K, Sugiura S, Yoshimura K, Kadowaki T, Nagai R. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nat Med. 2009; 15:914–20. [PubMed: 19633658]

20. Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, Nayer A, Lee J, Goldfine AB, Benoist C, Shoelson S, Mathis D. Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nat Med. 2009; 15:930–9. [PubMed: 19633656]

21. Wu D, Molofsky AB, Liang HE, Ricardo-Gonzalez RR, Jouihan HA, Bando JK, Chawla A, Locksley RM. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. Science. 2011; 332:243–7. [PubMed: 21436399]

22. Meneghin A, Hogaboam CM. Infectious disease, the innate immune response, and fibrosis. J Clin Invest. 2007; 117:530–8. [PubMed: 17332880]

23. Wynn TA. IL-13 effector functions. Annu Rev Immunol. 2003; 21:425–56. [PubMed: 12615888]

24. Donaldson DD, Whitters MJ, Fitz LJ, Neben TY, Finnerty H, Henderson SL, O'Hara RM Jr, Beier DR, Turner KJ, Wood CR, Collins M. The murine IL-13 receptor alpha 2: molecular cloning, characterization, and comparison with murine IL-13 receptor alpha 1. J Immunol. 1998; 161:2317–24. [PubMed: 9725226]
25. Hilton DJ, Zhang JG, Metcalf D, Alexander WS, Nicola NA, Willson TA. Cloning and characterization of a binding subunit of the interleukin 13 receptor that is also a component of the interleukin 4 receptor. Proc Natl Acad Sci U S A. 1996; 93:497–501. [PubMed: 8552669]
26. Caput D, Laurent P, Kaghad M, Lelias JM, Lefort S, Vita N, Ferrara P. Cloning and characterization of a specific interleukin (IL)-13 binding protein structurally related to the IL-5 receptor alpha chain. J Biol Chem. 1996; 271:16921–6. [PubMed: 8663118]
27. Aman MJ, Tayebi N, Obiri NI, Puri RK, Modi WS, Leonard WJ. cDNA cloning and characterization of the human interleukin 13 receptor alpha chain. J Biol Chem. 1996; 271:29265–70. [PubMed: 8910586]
28. Wills-Karp M, Finkelman FD. Untangling the complex web of IL-4-and IL-13-mediated signaling pathways. Sci Signal. 2008; 1:pe55. [PubMed: 19109238]
29. McKenzie AN, Culpepper JA, de Waal Malefyt R, Briere F, Punnonen J, Aversa G, Sato A, Dang W, Cocks BG, Menon S, et al. Interleukin 13, a T-cell-derived cytokine that regulates human monocyte and B-cell function. Proc Natl Acad Sci U S A. 1993; 90:3735–9. [PubMed: 8097324]
30. McKenzie GJ, Emson CL, Bell SE, Anderson S, Fallon P, Zurawski G, Murray R, Grencis R, McKenzie AN. Impaired development of Th2 cells in IL-13-deficient mice. Immunity. 1998; 9:423–32. [PubMed: 9768762]
31. Wynn TA. Fibrotic disease and the T(H)1/T(H)2 paradigm. Nat Rev Immunol. 2004; 4:583–94. [PubMed: 15286725]
32. Aliprantis AO, Wang J, Fathman JW, Lemaire R, Dorfman DM, Lafyatis R, Glimcher LH. Transcription factor T-bet regulates skin sclerosis through its function in innate immunity and via IL-13. Proc Natl Acad Sci U S A. 2007; 104:2827–30. [PubMed: 17307869]
33. Blease K, Jakubzick C, Westwick J, Lukacs N, Kunkel SL, Hogaboam CM. Therapeutic effect of IL-13 immunoneutralization during chronic experimental fungal asthma. J Immunol. 2001; 166:5219–24. [PubMed: 11290806]
34. Fichtner-Feigl S, Strober W, Kawakami K, Puri RK, Kitani A. IL-13 signaling through the IL-13alpha2 receptor is involved in induction of TGF-beta1 production and fibrosis. Nat Med. 2006; 12:99–106. [PubMed: 16327802]
35. Lee CG, Homer RJ, Zhu Z, Lanone S, Wang X, Koteliansky V, Shipley JM, Gotwals P, Noble P, Chen Q, Senior RM, Elias JA. Interleukin-13 induces tissue fibrosis by selectively stimulating and activating transforming growth factor beta(1). J Exp Med. 2001; 194:809–21. [PubMed: 11560996]
36. Chiaramonte MG, Donaldson DD, Cheever AW, Wynn TA. An IL-13 inhibitor blocks the development of hepatic fibrosis during a T-helper type 2-dominated inflammatory response. J Clin Invest. 1999; 104:777–85. [PubMed: 10491413]
37. Zhu Z, Homer RJ, Wang Z, Chen Q, Geba GP, Wang J, Zhang Y, Elias JA. Pulmonary expression of interleukin-13 causes inflammation, mucus hypersecretion, subepithelial fibrosis, physiologic abnormalities, and eotaxin production. J Clin Invest. 1999; 103:779–88. [PubMed: 10079098]
38. Kaviratne M, Hesse M, Leusink M, Cheever AW, Davies SJ, McKerrow JH, Wakefield LM, Letterio JJ, Wynn TA. IL-13 activates a mechanism of tissue fibrosis that is completely TGF-beta independent. J Immunol. 2004; 173:4020–9. [PubMed: 15356151]
39. Sun K, Kusminski CM, Scherer PE. Adipose tissue remodeling and obesity. J Clin Invest. 2011; 121:2094–101. [PubMed: 21633177]
40. Divoux A, Tordjman J, Lacasa D, Veyrie N, Hugol D, Aissat A, Basdevant A, Guerre-Millo M, Poitou C, Zucker JD, Bedossa P, Clement K. Fibrosis in human adipose tissue: composition, distribution, and link with lipid metabolism and fat mass loss. Diabetes. 2010; 59:2817–25. [PubMed: 20713683]
41. Khan T, Muise ES, Iyengar P, Wang ZV, Chandalia M, Abate N, Zhang BB, Bonaldo P, Chua S, Scherer PE. Metabolic dysregulation and adipose tissue fibrosis: role of collagen VI. Mol Cell Biol. 2009; 29:1575–91. [PubMed: 19114551]

42. Halberg N, Khan T, Trujillo ME, Wernstedt-Asterholm I, Attie AD, Sherwani S, Wang ZV, Landskroner-Eiger S, Dineen S, Magalang UJ, Brekken RA, Scherer PE. Hypoxia-inducible factor 1alpha induces fibrosis and insulin resistance in white adipose tissue. Mol Cell Biol. 2009; 29:4467–83. [PubMed: 19546236]

43. Keophiphath M, Achard V, Henegar C, Rouault C, Clement K, Lacasa D. Macrophage-secreted factors promote a profibrotic phenotype in human preadipocytes. Mol Endocrinol. 2009; 23:11–24. [PubMed: 18945811]

44. Hoffmann KF, Cheever AW, Wynn TA. IL-10 and the dangers of immune polarization: excessive type 1 and type 2 cytokine responses induce distinct forms of lethal immunopathology in murine schistosomiasis. J Immunol. 2000; 164:6406–16. [PubMed: 10843696]

45. Gurujeyalakshmi G, Giri SN. Molecular mechanisms of antifibrotic effect of interferon gamma in bleomycin-mouse model of lung fibrosis: downregulation of TGF-beta and procollagen I and III gene expression. Exp Lung Res. 1995; 21:791–808. [PubMed: 8556994]

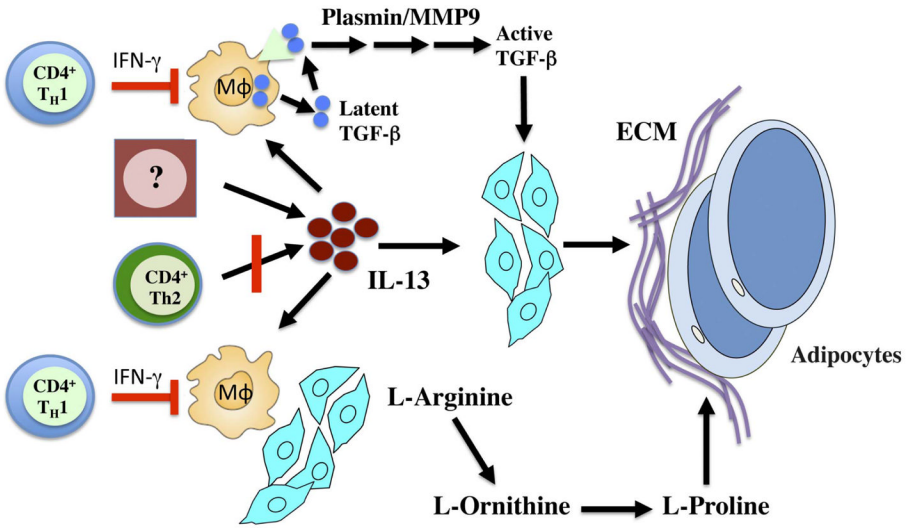

Figure 1. Alterations of immune cells with obesity regulate the inflammatory microenvironment in adipose tissue

Alternatively activated M2 macrophages, Th2 $CD4^+$ T cells, regulatory $CD4^+$ T cells (Treg) and eosinophils are dominant immune cells in adipose tissue of lean mice. These cells secrete anti-inflammatory cytokines such as IL-4 and IL-10 to suppress inflammation and maintain insulin sensitivity in adipose tissue. In obese mice, the composition of immune cells is dynamically shifted to enhance inflammatory responses in adipose tissue. Classically activated M1 macrophages, Th1 $CD4^+$ T cells, effector $CD8^+$ T cells, mast cells and B cells are increased and produce inflammatory cytokines such as TNF-α and IFN-γ and autoantibodies resulting in insulin resistance.

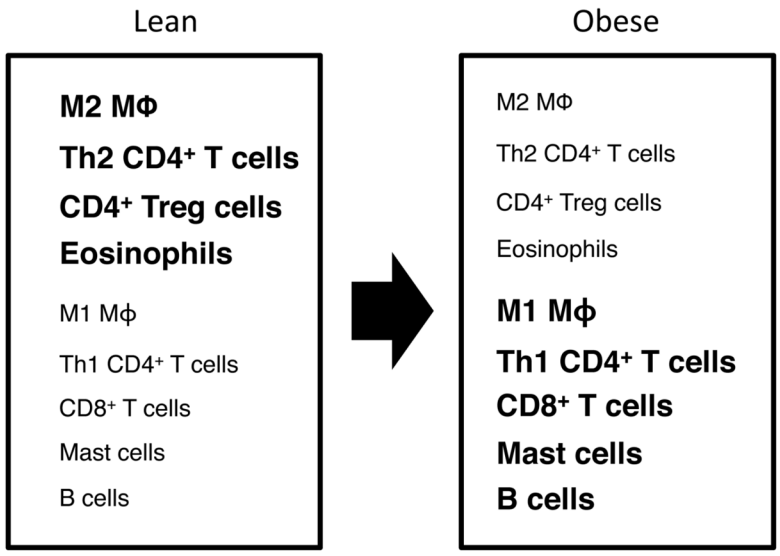

Figure 2. IL-13 and TGF-β might mediate independently or cooperatively to promote fibrosis in adipose tissue

In classical lung and liver fibrosis, IL-13 produced by Th2 $CD4^+$ T cells stimulates macrophages to produce TGF-β. Intracellular processing of prepro-TGF-β generates latent TGF-β, and secreted latent TGF-β binds to its receptor, CD36. Active TGF-β generated by plasmin and MMP-9 dependent degradation of LAP stimulates TGF-β receptors expressed in fibroblasts to produce ECM. IL-13 might directly activate the collagen-producing machinery in fibroblasts as fibroblasts express IL-13 receptors. IL-13 can also activate macrophages and/or fibroblasts to express Arginase-1 to increase L-proline, which promotes collagen production and fibrosis. IFN-γ produced by Th1 $CD4^+$ T cells antagonizes these pathways as IFN-γ inhibits the differentiation of alternatively activated macrophages and Th2 $CD4^+$ T cells. Genetically modified and HFD-induced obese mice show enhanced adipose tissue fibrosis and IFN-γ producing Th1 $CD4^+$ T cells are increased. In contrast Th2 $CD4^+$ T cells are significantly decreased in obese adipose tissue suggesting that the main source of IL-13 may be non-Th2 $CD4^+$ T cells. This schematic model was adapted from Wynn *et al.* (31).