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Role of Adipose Tissue as an Inflammatory Organ in Human Diseases

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Reviews on the inflammatory role of adipose tissue outside the field of metabolism are rare. There is increasing evidence provided by numerous basic research studies from nearly all internal medicine subspecializations that adipocytes and adipocytokines are involved in primary inflammatory processes and diseases. Therefore, it is the aim of the present review to discuss and to summarize the current knowledge on the inflammatory role of adipocytokines and special types of regional adipocytes such as retroorbital, synovial, visceral, subdermal, peritoneal, and bone marrow adipocytes in internal medicine diseases. Future clinical and therapeutic implications are discussed. (*Endocrine Reviews* 27: 449–467, 2006)

I. Introduction and Focus

DURING THE PAST 10 yr, the understanding of the physiological and pathophysiological role of the adipocyte has been completely changed. Once considered to be a passive type of connective tissue storing excess energy as triglycerides, adipose tissue has now been established as a real endocrine organ coupling (neuro)-endocrine and metabolic signaling. This new point of view was reviewed excellently by Kershaw and Flier (1). Secretory products of preadipocytes and mature adipocytes, the so-called adipocytokines (2), clearly regulate energy homeostasis, appetite/satiety, reproduction, and insulin sensitivity and influence neuroendocrine, endothelial, immunological, hematological, angiogenetic, and vascular functions in an endocrine, paracrine, and autocrine manner. Adipocytokines such as adiponectin are currently discussed as new drug targets in treating atherosclerosis and single components of the metabolic syndrome (3), such as visceral obesity, hypertension, insulin resistance, type 2 diabetes mellitus, and dyslipidemia (4).

In contrast to numerous and excellent publications describing the role of adipose tissue and adipocytokines in metabolic syndrome and atherosclerosis (5, 6), reviews on the inflammatory role of adipose tissue outside the field of metabolism are rare (7–9). However, visceral obesity is characterized by a C-C motif chemokine receptor-2-mediated infiltration of adipose tissue by monocytes (9, 10) and is being regarded more and more as a chronic and low-grade state of inflammation causing whole body insulin resistance (11). There is increasing evidence provided by numerous basic research studies from nearly all internal medicine subspecializations that adipocytes and adipocytokines are involved in primary inflammatory processes and diseases (12, 13). Comprehensive and interdisciplinary reviews summarizing the inflammatory role of "alternative" stores of adipose tissue are currently not available.

Therefore, it is the aim of the present review to discuss and to summarize the inflammatory role of adipocytokines and special types of regional adipocytes, such as retroorbital, synovial, visceral, subdermal, peritoneal, and bone marrow adipocytes in internal medicine diseases (Table 1). Due to the criteria mentioned above, it is not the aim of the present review to discuss the role of adipocytes in the context of visceral obesity, insulin resistance, type 2 diabetes mellitus, hypertension, dyslipidemia, metabolic syndrome, atherosclerosis, or lipodystrophic syndromes.

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Abbreviations: ADD1/SREBP1, adipocyte determination- and differentiation-dependent factor-1 / sterol regulatory element binding protein-1; AdipoR1, adiponectin receptor type 1; AdipoR2, adiponectin receptor type 2; BMI, body mass index; C/EBP, CCAAT enhancer binding protein; CFU, colony-forming unit; CORS-26, collagenous repeat containing sequence of 26 kDa protein; CRP, C-reactive protein; CT, computed tomography; Foxa2, forkhead box A2; Foxo1, forkhead box O1; GATA-2, GATA binding protein-2; HMW, high molecular weight; IBMX, isobutylmethylxanthine; KLF, Krüppel-like transcription factor; Krox20, Krox-20 homolog *Drosophila*, previously EGR2 early growth response 2; LPL, lipoprotein lipase; LPS, lipopolysacharide; MCP-1, monocyte chemoattractant protein-1; M-CSF, macrophage colony-stimulating factor; MMP, matrix metalloproteinase; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor-κB; OA, osteoarthritis; PPAR, peroxisome proliferator-activated receptor; PPRE, PPAR response element; Pref-1, preadipocyte factor-1; RA, rheumatoid arthritis; RELM, resistin-like molecule; RXRα, retinoid X receptor α; sFRP, secreted frizzled related protein-1; STAT, signal transducer and activator of transcription.

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TABLE 1. Role of different adipose tissue depots, regional adipocytes, and adipocytokines in the pathophysiology of inflammatory human diseases

Type of adipose tissue/ adipocytes	Internal medicine subspecialization	Inflammatory disease
Synovial adipocytes/infrapatellar fat pad	Rheumatology	OA, RA
Mesenteric/visceral adipocytes	Gastroenterology	Mesenteric panniculitis, acute pancreatitis
	Hepatology	NASH/NAFLD
Creeping fat	Gastroenterology	Crohn's disease
Peritoneal adipocytes	Gastroenterology	Peritonitis, peritoneal tumor spread
Retroorbital adipocytes	Endocrinology	Graves' ophthalmopathy
Subdermal adipocytes	Endocrinology	Pretibial dermopathy
Bone marrow adipocytes	Hematology	Hematopoesis, leukemia
	Osteology	Osteoporosis, bone diseases
Secreted adipocytokines	Immunology	Monocyte/macrophage function
	Hepatology	NASH/NAFLD
All adipose tissues	Infectiology	Reservoir of microbial infection

Due to the high number of references supporting the items mentioned in the table, the detailed publications must be obtained from the respective sections within the text.

II. From the Mesenchymal Stem Cell toward Adipose Tissue

A. Cellular development

Adipocytes differentiate from a pluripotent mesenchymal stem cell (14) that has the potential for chondrogenic, osteogenic, myogenic, and adipogenic differentiation (15, 16). Recent studies demonstrated that pluripotent stem cells can be obtained from stromal cells isolated from mature adipose tissue (17). The subsequent development and differentiation into mature adipocytes is highly regulated and undergoes uniform steps (Fig. 1) of commitment, cell contact, mitosis, clonal expansion, growth arrest, and maturation (5, 18–20).

The commitment (determination) of the pluripotent mesenchymal stem cell to the adipocyte lineage (15) is triggered mainly by mechanisms yet to be identified and creates an adipoblast. The first step in adipogenesis is the reentry of growth-arrested preadipocytes into the cell cycle and the subsequent clonal expansion. This step is regulated by the phosphorylation state of the tumor suppressor gene Rb (retinoblastoma protein), its interaction with the transcription factor E2F, and the subsequent activation/deactivation of cyclin-dependent kinases (21). After cell-to-cell contact, an early preadipocyte of first order arises and expresses early genes such as α_2Col6 (α_2 chain of collagen 6), IGF-I, and lipoprotein lipase (LPL). After mitosis and clonal expansion, the preadipocyte of second order undergoes growth arrest. Only these growth-arrested preadipocytes can differentiate into mature adipocytes. This ability for further differentiation depends on the expression of early and intermediate markers of differentiation (22, 23), such as the typical adipogenic transcription factors CCAAT-enhancer binding protein (C/EBP) β, C/EBPδ, peroxisome proliferator activated receptor (PPAR) γ_2, and adipocyte determination- and differentiation-dependent factor-1 (ADD1)/sterol regulatory element binding protein-1 (SREBP1). As a consequence of these transcriptional main events, immature adipocytes begin to accumulate lipid droplets and to express late markers

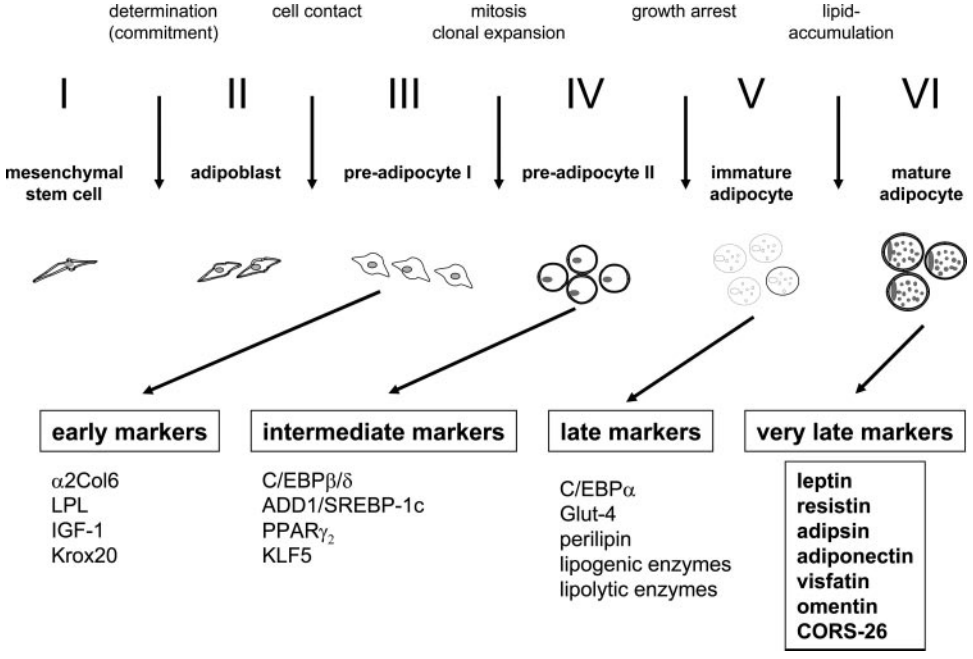

FIG. 1. Cellular development and gene expression profile during adipocyte differentiation. Glut-4, Glucose transporter-4.

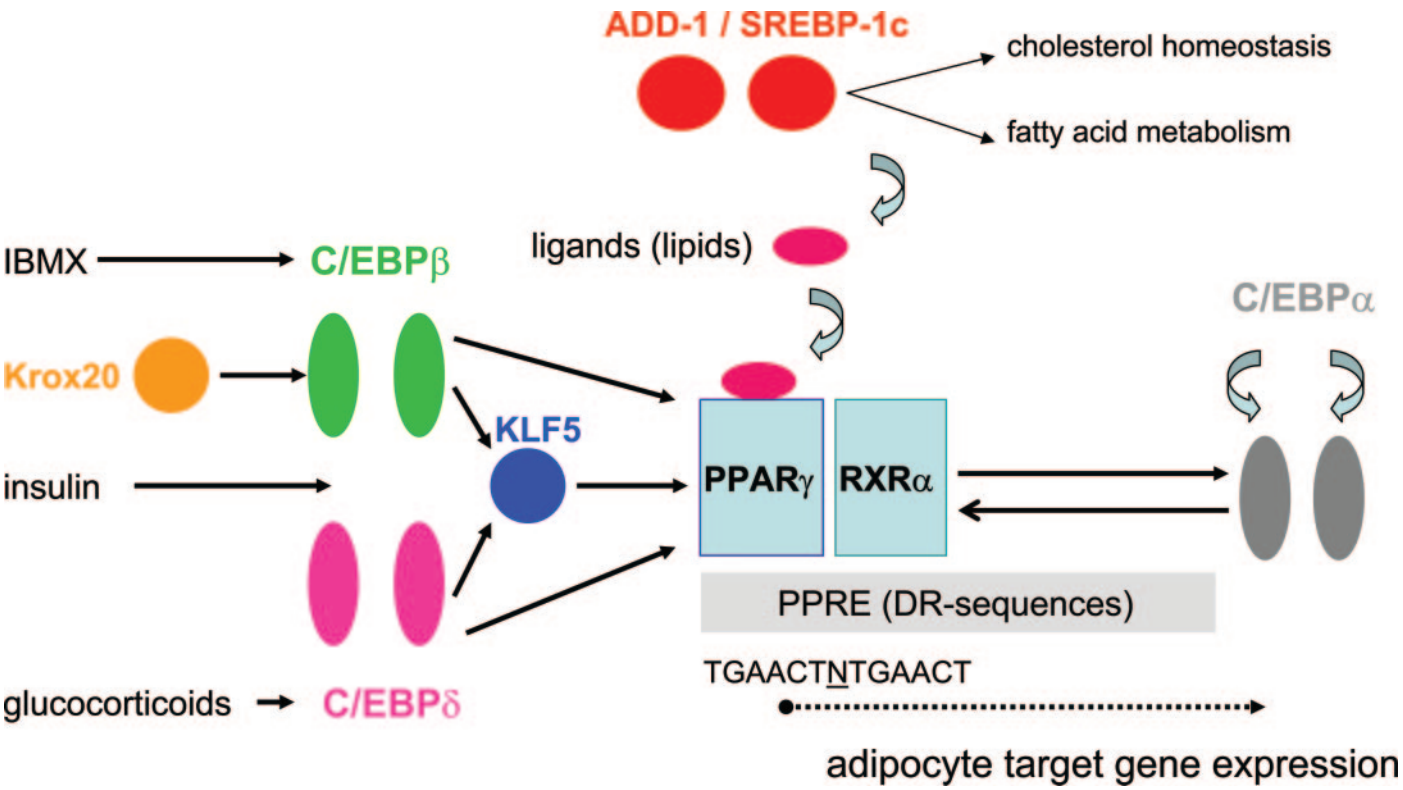

FIG. 2. Transcriptional control of adipocyte differentiation. Stimulatory factors regulating adipogenesis. Hormonal stimuli are necessary for the induction of adipocyte differentiation. The different stages of adipocyte differentiation are controlled by a network of stimulatory and adipogenic transcription factors.

of differentiation such as C/EBPα, glucose transporter-4, perilipin, and lipogenic and lipolytic enzymes. During the last decade, it has become evident that these mature adipocytes are characterized by the expression and secretion of highly specific and very late markers of differentiation such as leptin (24), adiponectin (4), resistin (25), visfatin (26, 27), omentin (28), adipsin (29), and collagenous repeat containing sequence of 26 kDa protein (CORS-26) (30). These molecules not only regulate energy, glucose, and lipoprotein metabolism (31) but also represent pro- and antiinflammatory mediators of the adipose tissue (7, 13). In a general context of inflammation, adiponectin (32, 33) and CORS-26 (34) seem to represent more antiinflammatory adipocytokines, whereas resistin (35) and leptin (36) seem to act as proinflammatory adipocytokines.

B. Transcriptional regulation

The cellular and transcriptional mechanisms controlling adipogenesis have been elucidated in detail mainly in several rodent cell lines (*e.g.*, 3T3-L1 preadipocytes) and also human adipocytes. The detailed molecular mechanisms of adipocyte differentiation are characterized by a complex and highly regulated interplay of stimulatory (Fig. 2) and inhibitory (Fig. 3) transcription factors during certain phases of the differentiation process. The molecular concept of adipocyte differentiation has been summarized in several excellent reviews (5, 18–21, 37–40). Although several transcriptional key events regulating the differentiation of preadipocytes into mature adipocytes have been identified in the last decade, master genes committing the multipotent mesenchymal stem cell to adipoblasts are still waiting to be discovered (15). Most recently, transcriptional coactivator with PDZ-binding motif (TAZ) was identified as an early "molecular rheostat" modulating mesenchymal stem cell differentiation (41).

Adipocyte differentiation is characterized by two contrary transcriptional events (transcriptional remodeling): the up-regulation of stimulatory transcriptional regulators during adipogenic conversion (Fig. 2) and the down-regulation of inhibitory transcriptional regulators in early preadipocytes and adipoblasts (Fig. 3).

The zinc finger transcription factor Krox20 (Krox-20 homolog *Drosophila*, previously EGR2 early growth response 2) is expressed in preadipocytes and represents one of the earliest factors becoming induced during adipogenesis (42). Krox20 acts upstream of the C/EBPβ gene by transactivation of the C/EBPβ gene promoter (43). Hormonal stimuli such as insulin and glucocorticoids or isobutylmethylxanthine (IBMX) trigger adipogenic differentiation by causing a transient induction of C/EBPβ and C/EBPδ expression during the early phase of adipogenesis at the stage of the preadipocyte (dexamethasone increases C/EBPδ gene expression, whereas isobutylmethylxanthine increases C/EBPβ gene expression). These C/EBP transcription factors (44) consist of a C terminal, a basic DNA binding domain, and a leucine zipper domain mediating homo-/heterodimerization.

C/EBPβ and C/EBPδ together induce the expression of Krüppel-like transcription factor (KLF) 5, a zinc finger transcription factor (42) that activates the PPARγ_2 promoter (45).

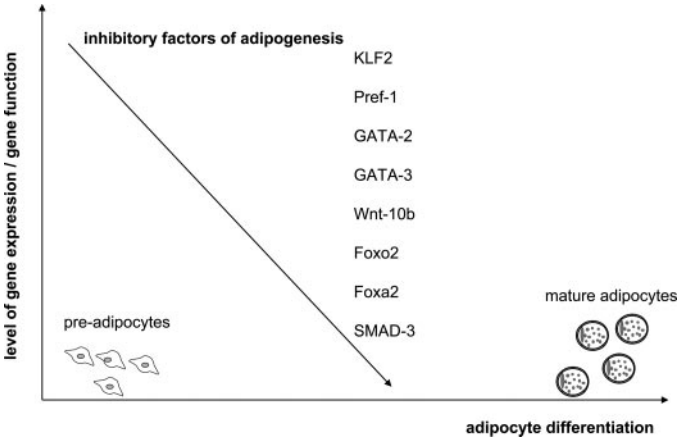

FIG. 3. Transcriptional control of adipocyte differentiation. Inhibitory factors regulating adipogenesis. The down-regulation of gene expression/gene function of inhibitory factors normally blocking adipocyte differentiation in preadipocytes is a prerequisite of the adipogenic differentiation program. Wnt-10b, Wingless-type MMTV integration site family member 10b.

The simultaneous activation of C/EBPβ, C/EBPδ, and KLF5 strongly induces the expression of PPARγ_2. PPARγ_2 (46, 47) belongs to the ligand-activated nuclear receptors of the thyroid, steroid, and vitamin D receptor family and is characterized by a ligand-activation domain and a DNA binding domain consisting of two zinc finger motifs. PPARγ_2 represents the transcriptional master regulator of adipocyte differentiation, and, together with C/EPBα, it is responsible for the maintenance of the fully differentiated phenotype. In parallel, as yet unidentified lipid ligands are produced via ADD1/SREBP1, which additionally activates PPARγ_2. ADD1/SREBP1 (48) belongs to the family of basic helix-loop-helix transcription factors possessing a dual DNA specificity by binding to E-box sequences and non-E-box sequences (sterol responsive elements).

PPARγ_2 is only active as an obligate heterodimer with retinoid X receptor (RXR) α. This complex binds to specific recognition elements, PPAR response elements (PPREs), within the promoter regions of adipocyte-specific target genes. These PPREs consist of a so-called *DR-1-Motif* [TGAACTNTGAACT] (direct repeat of the nuclear receptor hexameric DNA core recognition motif spaced by one nucleotide). After induction and activation of PPARγ_2, the expression of C/EBPα is induced. C/EBPα can be regarded as a transcriptional master regulator of late adipocyte differentiation, and it is responsible for the maintenance of the fully differentiated phenotype. C/EBPα induces its own expression as well as the transactivation of PPARγ_2 via specific C/EBP binding sites in the promoter regions of both genes (21).

Besides this positive cascade of transcriptional activation, inhibitory transcription factors expressed in preadipocytes become down-regulated because otherwise they would inhibit the differentiation program (Fig. 3). Among these inhibitory pathways of adipocyte differentiation, the zinc finger transcription factors GATA-binding protein-2 and -3 (GATA-2 and GATA-3) (49) function as inhibitors of adipogenesis by repressing PPARγ_2 promoter activity (50) and by forming protein complexes with C/EBPα and C/EBPβ (51). An inhibition of preadipocyte to adipocyte transition is also exerted by activation of the Wnt signaling cascade (52, 53). KLF2 also represents an inhibitory transcription factor that is expressed in preadipocytes and becomes down-regulated during adipogenesis. KLF2 does not affect the commitment of the mesenchymal stem cell, but it maintains the preadipocyte state and inhibits the transition into adipocytes (54). KLF2 functions as an inhibitory transcription factor by repressing PPARγ_2 promoter activity (55) and by restoration of preadipocyte factor-1 (Pref-1) (54). Pref-1, one of the epidermal growth factor-like proteins, is a secreted preadipocyte factor synthesized as a membrane protein that undergoes cleaving of its ectodomain to generate a soluble form (56). Pref-1 inhibits adipocyte differentiation and is induced by dexamethasone and down-regulated during adipogenesis. Other recently described signaling molecules negatively interfering with adipogenesis are forkhead box O1 (Foxo1) and A2 (Foxa2) , mothers against decapentaplegic *Drosophila* homolog 3 (SMAD-3), and wingless type MMTV integration site family member 10b (Wnt-10b) (53, 57).

Efforts to understand the highly regulated balance between positive and negative intracellular and extracellular factors governing adipogenesis are still in progress and may have important therapeutical implications.

III. Adipocytes and Adipocytokines in Inflammatory Diseases

A. Rheumatology

1. Adipose tissue-derived effector molecules in arthritis and rheumatic diseases. Less than a decade ago, adipose tissue-derived effector molecules began to be investigated in rheumatological disorders. In rheumatoid arthritis (RA), leptin was found to be present in serum, and it correlated with percentage body fat in some patient populations but not with disease activity (58) or individual parameters of inflammation, such as erythrocyte sedimentation rate and C-reactive protein (CRP) (59). Although there is a direct link between key inflammatory molecules in arthritides such as IL-6, TNF-α, and leptin, chronic inflammation appears to reduce plasma leptin levels in patients with RA (60), an effect that might be based on an intensive consumption in the arthritic joint (61). In osteoarthritis (OA) patients, leptin could also be found in synovial fluid and correlated to a similar extent as in RA with the body mass index (BMI) of the patients (62). In juvenile arthritis, leptin was a marker for the nutritional status of the patient and could not be used for differentiation of active and inactive disease (63). In less joint-associated rheumatic diseases such as systemic lupus erythematosus, the affected patients showed higher serum leptin levels than BMI-adjusted healthy controls, but similar to RA and OA, there was also no correlation between disease activity and leptin serum levels (64). The only disease with a positive correlation between activity and leptin levels at present is Behçets disease, a common vasculitis around the Mediterranean and the Near and Far East (65).

Although articular and synovial adipose tissue is one of the ubiquitous components of a human joint, little is known about its local function, especially with regard to arthritis.

However, recent studies have revealed novel links between adipose tissue, adipocytokines (*e.g.*, adiponectin and resistin), and arthritides (61). In particular, classical adipocytokines such as adiponectin (66) and the adiponectin-paralogous gene CORS-26 (30) are expressed both by synovial fibroblasts and directly by articular adipocytes. However, it is important to emphasize that many proinflammatory cytokines (IL-6 and TNF-α) and adipocytokines (leptin and resistin) are also produced by articular nonadipocytic cells, such as chondrocytes or immigrated inflammatory cells, and that point has to be considered by interpreting data derived from total articular tissue or synovial fluid.

Ushiyama *et al.* (67) have demonstrated the presence of proinflammatory cytokines and growth factors in the infrapatellar fat pad from patients with OA, and we could show that the adipocytokines adiponectin and resistin are present in high levels in synovial fluid (and not in serum) of patients with RA and OA (68). Furthermore, not only adipocytes but also other activated cells of the mesenchymal lineage such as synovial fibroblasts within the synovial lining, the perivascular area, and the inflamed sublining are main producers of adiponectin. Not only could this property be maintained in culture, but the respective adiponectin receptors necessary to transfer the adiponectin-dependent signals into the articular effector cells appeared to be characteristic for mesenchymal cells, such as articular fibroblasts, periarticular adipocytes, cartilage, and bone. These cells can express type I and type II adiponectin receptors from the embryonic state (69) to the adult human organism. In addition, novel members of the recently discovered TNF/C1q superfamily are present in arthritic synovium. For example, CORS-26 could also be found in murine and human synovial adipocytes (70). Interestingly, its chromosomal localization was mapped to the chromosome locus 15A2, which links this adipokine directly to experimental arthritis, because the linkage loci for both MRL lpr/lpr- and proteoglycan-induced arthritis (two experimental animal models for arthritis) are positioned within the same genomic region.

According to current data, one of the main producers of articular leptin is chondrocytes (62, 71), which appear to be part of a feedback loop because chondrocytes also express the leptin receptor OB-Rb. Moreover, a negative effect of leptin on cartilage metabolism has been reported. When acting in combination with interferon-γ, nitric oxide synthesis in chondrocytes is significantly increased (72). Leptin levels also correlate with osteophytic destruction and growth factor IGF-I and TGFβ1 expression. Interestingly, the altered bone formation stimulated by leptin is not only based on its antiosteogenic potential, but this inhibitory capability appears to be directly linked to effects on mesenchymal stem cells, stromal precursor cells, and the sympathetic nervous system via high-affinity leptin receptors (73).

Adipocytokines such as adiponectin have significant effects on the metabolism of articular fibroblasts, and this stimulatory capacity appears to be highly selective, because only two of the main mediators of pathophysiology in RA, *i.e.*, IL-6 and proMMP-1, are being synthesized under the influence of adiponectin, whereas most others, including proinflammatory substances such as IL-1, TNFα, vascular endothelial growth factor, and TGFβ as well as protective cytokines such as IL-4 and IL-10, are not affected (66, 74). However, the only pathway known to be involved in adiponectin receptor signaling as well as in key pathways operative in RA synovial fibroblasts or osteoblasts is the p38 MAPK pathway (75). This selectivity is further supported by the finding that neither protein kinase A nor protein kinase C enhances any of these effector molecules in rheumatoid synovial fibroblasts that were mentioned above. Of note, at least *in vitro* the phenotypic difference between fibroblasts and adipocytes appears marginal as cytokines are capable of transforming fibroblasts into adipocytes (76), and leptin can stimulate the differentiation of mesenchymal stem cells into osteoblasts, chondrocytes, and adipocytes (77). Resistin, on the other hand, was able to up-regulate IL-6 and TNFα in human peripheral blood mononuclear cells and induced severe arthritis when injected in nonarthritic murine joints (78). In contrast to adiponectin, resistin regulation was found to be predominantly nuclear factor-κB (NF-κB)-dependent (78).

2. Animal models. Experimental murine models could show that leptin is directly involved in immune phenomena in arthritis. Leptin-deficient ob−/ob− mice developed a substantially less active antigen-induced arthritis than wild-type mice, and similar results were seen in leptin receptor-deficient mice (79). These effects were paralleled by lower concentrations of the proinflammatory cytokines TNFα and IL-1β, a switch to joint-protective Th2 cytokines, and a decreased proliferative response when performing an antigen challenge of lymph node cells (79). Interestingly, although secondary cellular immune responses were also diminished, which was illustrated by a reduced antigen-specific T cell and B cell response in combination with higher IL-10 and lower interferon-γ production, no reduction of cartilage degradation could be observed. The latter finding was supported by the lack of leptin-dependent effects on zymosan-induced arthritis, a murine arthritis model that develops independent of adaptive immunity (80). In addition, the expression of chemokines monocyte chemoattractant protein (MCP)-1 and macrophage inflammatory protein-1α by adipocytes and the presence of the novel CC-chemokine macrophage inflammatory protein-related protein-2 in murine fat pads indicates that adipocytes may even be responsible for chemoattraction of other inflammatory cells (81).

Clinical and therapeutical implications: As outlined above, leptin is directly linked to the neuroendocrine system. In patients with RA and systemic lupus erythematosus, serum levels of androstenedione correlated negatively with the serum levels of leptin and might be responsible, at least in part, for the known hypoandrogenicity in these patients (82). Conversely, although not related to systemic inflammatory parameters, leptin appears to exert protective effects in septic arthritis, because recombinant leptin reduced both inflammation and articular destruction in *Staphylococcus aureus*-induced arthritis without reducing the viability of bacteria *in vivo* (83). Medication also has an effect on serum leptin levels, but this effect depends on the type of the antiarthritic drug, because it could be shown that the majority of disease-modifying antiarthritic drugs were associated with low leptin levels, whereas patients under therapy with methotrexate showed higher leptin plasma concentrations (61), and anti-TNF therapy did not alter leptin serum levels (60).

In contrast to leptin, adiponectin exerts significant proinflammatory and matrix-degrading effects in arthritis (66). Moreover, it can no longer be regarded as a strictly adipocyte-specific protein, at least not in the context of chronic inflammation. In human RA, adipocytes might be the key interaction partners for the matrix-degrading synovial fibroblasts (84), which are specifically active at sites of destruction (85). The hypothesis is supported by the finding that adiponectin is a strong stimulator with regard to the synthesis of cytokines, growth factors, and matrix metalloproteinases (MMPs). Moreover, it is likely that the ameliorating effect on inflammatory and joint-destructive mechanisms, especially on IL-6 and MMP-1-dependent pathways of TNF-inhibitors is, at least in part, based on an anti-adipocytokine effect (66, 86). This effect appears restricted to adiponectin, because treatment with TNF inhibitors did not alter leptin plasma levels in patients with RA (60).

Taken together, the current data support the idea that (peri)articular adipose tissue and adipocytokines can no longer be regarded innocent bystanders in arthritides because they modulate substantially the expression of local synovial cytokines and matrix-degrading enzymes and thus may also become an attractive candidate target for novel antiarthritic strategies.

B. Gastroenterology

1. Crohn's disease. Patients suffering from Crohn's disease regularly develop an accumulation of intraabdominal, mesenteric adipose tissue from the onset of the disease. Accordingly, mesenteric obesity represents a basic and common feature of Crohn's disease (87) that cannot simply be diagnosed by measuring the patient's BMI. However, this increased mesenteric adipose tissue mass is nowadays routinely diagnosed by computed tomography (CT) and magnetic resonance imaging techniques (87, 88). During surgery, this special type of mesenteric adipose tissue presents as tissue hypertrophy, showing signs of inflammation and an increased stiffness during tissue palpation. Regional lymphadenopathy might also be present. Dr. Burril B. Crohn, who gave his name to this chronic inflammatory bowel disease, initially described the changes in the appearance of the mesenteric adipose tissue. The connective and adipose tissue changes contiguous to the involved intestine in Crohn's disease are characterized by (13, 89): 1) mesenteric fat hypertrophy; 2) creeping fat, meaning fat creeping upon the bowel; 3) fat wrapping, meaning enveloping the bowel surface/circumference; 4) fibrofatty proliferation, macrophage infiltration; 5) regional lymphadenopathy; 6) tissue fibrosis; 7) perivascular and transmural inflammation; and 8) intimal/medial thickening of vessels (90–94).

Interestingly, fat wrapping/creeping fat correlates with ulceration, stricture formation, transmural inflammation, wall thickness, and internal bowel diameter (90).

It is a matter of controversy (13, 89) whether the development of creeping fat is a causative or secondary phenomenon (13, 89) to the underlying intestinal disease (Table 2). Some groups interpret fat wrapping as a phenomenon secondary to the process of transmural inflammation and the subsequent release of proinflammatory cytokines such as TGF-β_1 and TNF-α (90, 93, 95, 96) from the intestinal mucosa and from macrophages present within the adjacent soft tissue. As a consequence, PPARγ becomes activated and could then promote adipose tissue hypertrophy that could build a barrier against the transmural inflammation.

In contrast, an increasing body of evidence suggests that the mesenteric adipose tissue plays a more active role in the pathogenesis of creeping fat and mesenteric inflammation (13, 89, 97). Adipocytes not only respond to proinflammatory cytokines but also are known to secret proinflammatory and antiinflammatory mediators such as TNF-α (87), IL-10 (98), vascular endothelial growth factor (99), leptin (100), macrophage-colony-stimulating factor (M-CSF) (101), regulated upon activation, normal T cell expressed and secreted (RANTES) (CCL5) (98), and adiponectin (102). The specific overexpression of TNF-α (87), leptin (100), M-CSF (101), and adiponectin (102) in creeping fat derived from patients with Crohn's disease argues for a more active role of the adipose tissue. Furthermore, it was demonstrated that mesenteric adipocytes secret higher amounts of TNF-α than mesenteric monocytes/macrophages (87). Similarly, leptin mRNA levels were reported to be significantly higher in mesenteric adipose tissue from patients with either Crohn's disease or ulcerative colitis when compared with control patients with colonic carcinoma as a noninflammatory disease (100). Luminal application of leptin can even cause colonic epithelial wall damage and neutrophil inflammation (103).

TABLE 2. Arguments for a causative or a secondary role of mesenteric adipose tissue hypertrophy in Crohn's disease

Creeping fat: arguments for a causative role	Creeping fat: arguments for a secondary role
Mesenteric fat hypertrophy present at onset of disease	Transmural inflammation might cause adjacent adipose tissue hypertrophy
Axial polarity of inflammation and ulcers along the mesenteric border	Mesenteric fat hypertrophy with a putative barrier function
Adipocytes secreting both pro- and antiinflammatory mediators	Chronic intestinal cytokine release
Amount of TNF-α secretion higher from mesenteric adipocytes than from macrophages	Chronic lymphoid tissue cytokine release
Up-regulation of PPARγ expression drives adipogenesis	Perinodal adipose tissue hypertrophy
Secretion of chemoattractants from adipocytes (MCP-1, M-CSF) attracts monocytes into adipose tissue	Regional lymphadenopathy

There is a controversial discussion as to whether creeping fat in Crohn's disease is a primary and causative phenomenon (*left column*) or a secondary phenomenon simply caused by the chronic and transmural inflammation of the gut (*right column*). Further information regarding this controversy can be found in *Section III.B* and recent reviews (9, 13, 89).

Clinical and therapeutical implications: The activation of PPARγ by synthetic ligands such as thiazolidinediones reduces proinflammatory TNF-α and leptin gene expression and increases antiinflammatory adiponectin gene expression in adipocytes (104). Furthermore, PPARγ activation diminishes the activation of inflammatory response genes by decreasing the activity of the NF-κB, activator protein-1, and signal transducer and activator of transcription (STAT)-1 transcription factor pathways (105). Hence, PPARγ activation fosters an antiinflammatory microenvironment within mesenteric adipose tissue. In detail, activating ligands of PPARγ were shown to inhibit the expression of proinflammatory cytokines such as IL-1β, IL-2, IL-6, IL-8, MCP-1, TNF-α, and MMPs by mechanisms including transcriptional regulation and nontranscriptional interference with signaling pathways such as NF-κB (p65, p50), activator protein-1 (fos/jun), MAPK cascade, and STAT-1/STAT-3 (105, 106). These observations have been made in different cell types such as monocyte/macrophages, endothelial cells, smooth muscle cells, and adipocytes. Because these cell types are abundantly expressed in the adipose tissue, the control function of the PPARγ/RXR heterodimer in inflammation (106) could provide the basis for potential therapeutic applications in inflammation-related diseases such as chronic inflammatory bowel disease (106, 107).

Recently, increasing data have pointed to this nuclear hormone receptor as a novel antiinflammatory mediator with broad therapeutic potential in ulcerative colitis and Crohn's (107, 108). The PPARγ ligands troglitazone and rosiglitazone were tested in an experimental animal model, the dextran sodium sulfate-induced colitis, and shown to inhibit the colonic inflammation, possibly by attenuating cytokine gene expression in colon epithelial cells via inhibiting the activation of NF-κB. Similarly, a gene therapy approach (109, 110) using PPARγ proved to be successful in the treatment of dextran sodium sulfate-induced colitis. Desreumaux *et al.* (107) were successful in ameliorating colitis in an experimental mouse model (trinitrobenzene sulfonic acid-induced colitis) by treatment with PPARγ and RXR ligands. Even in ischemia-induced colitis, PPARγ seems to mediate potent antiinflammatory effects (111).

2. Mesenteric panniculitis. Although there are numerous case reports and clinical descriptions, the pathophysiology of mesenteric panniculitis is completely unknown (112–115). The disease has been described by several synonyms such as Pfeiffer-Weber-Christian disease, mesenteric panniculitis, xanthogranulomatous mesenteritis, mesenteric lipodystrophy, retractile mesenteritis or, sclerosing mesenteritis). These terms mainly refer to the typical histopathological findings that characterize a special type of mesenteric inflammation without any involvement of the adjacent gut, lymph nodes, or vessels. The inflammatory soft tissue changes mostly affect the mesentery of the small bowel and are characterized by nonfocal lymphoplasmocytic infiltration, fat cell necrosis, foamy macrophages, and focal fibrosis (114). Thickening and retraction of the mesentery occur as a consequence and can be divided into three classes according to Kipfer *et al.* (113): diffuse thickening of the mesentery (type 1); single knotty thickenings at the mesentery root (type 2); and multiple knotty thickenings of the mesentery (type 3). Fat cell necrosis and lipid-laden macrophages (foam cells) are among the most characteristic and specific findings that could give insights into the pathophysiology of the disease. Whether fat cell necrosis occurs as a primary event triggered by yet unknown mechanisms or whether a primary and sterile (autoimmune?) inflammation causes fat cell necrosis is a matter of uncertainty. Although a severe and fatal disease course is possible (116), it mostly appears as an exclusion diagnosis of an intraabdominal tumor (112, 117) or as a differential diagnosis of uncharacteristic symptoms such as obstipation/diarrhea, ileus, weight loss, fever, and abdominal pain. Although radiological techniques have been significantly improved (118–121), diagnosis still remains a challenge.

Clinical and therapeutical implications: Whereas antibiotic treatment seems not to provide a successful therapeutic approach, surgery and immunosuppressants such as corticosteroids, azathioprine, or cyclophosphamide have been used successfully in more severe cases (122–125). There are no data on whether glitazone treatment might improve the clinical course of mesenteric panniculitis. Because PPARγ activation induces the expression of antiinflammatory genes in adipocytes (adiponectin) (126) and has antiinflammatory effects (127) on monocytes/macrophages or endothelium in the context of atherosclerosis (128), glitazone treatment might be a reasonable drug target (129) to be tested in clinical trials or individual patients because the disease is rather rare.

3. Acute pancreatitis. Whereas most patients with acute pancreatitis (130) recover without complications, about 10–20% (131, 132) will develop systemic (organ system failure) or local (necrosis, pseudocyst, abscess) complications. Because a variety of therapeutic strategies such as prophylactic antibiotic treatment, early enteral nutrition, endoscopic sphincterotomy, CT-guided drainage, or laparotomy are currently discussed (130), there is a considerable clinical interest in the prediction of severity and risk of necrosis (131, 133–138). Multiple factor scoring systems, including therapy-associated and patient-related factors based on anthropomorphical, clinical, biochemical, and physiological disturbance, have been developed such as the APACHE-II score (139, 140), the APACHE-O score (138), the Glasgow Coma Scale (GCS) (141), and the Ranson score (142). In addition, different radiological scoring systems (133, 143–146) describing the extent of pancreatic and extrapancreatic necrosis have been published, such as the Schröder score (145, 146), the pancreatic necrosis score (146), and the Balthazar score (133, 143, 144, 146).

Markers of trypsinogen activation (131, 135, 147) or the systemic release of cytokines (131, 134, 135, 137, 148, 149) such as IL-10 (150), IL-8 (151, 152), and IL-6 (150, 153) have been evaluated for their potential value in early severity prediction. In clinical praxis, serum glucose (150), serum calcium (150), CRP levels (136, 154), and hematocrit (155) have been reported to be the best widely available markers in predicting the severity of acute pancreatitis.

Obesity is associated with an increased risk of severe outcome in acute pancreatitis (154–157). Accordingly, adding a simple obesity score (by calculating the BMI) to the

APACHE-II score (APACHE-O score) (138) can provide a slightly greater predictive accuracy. This indicates that the adipose tissue compartment, especially the visceral adipose tissue, might play an important pathophysiological role in pancreatitis-associated morbidity and mortality. However, up to now there are no convincing data linking the amount of visceral adipose tissue directly with the clinical outcome of an acute pancreatitis.

Visceral adipose tissue-derived secretory factors might play a role during the clinical course of acute pancreatitis (158). Based on this hypothesis (158), peripancreatic fat cell necrosis could cause a massive release of adipocytokines possibly causing organ dysfunction. Moreover, if highly adipocyte-specific marker proteins such as leptin (36), adiponectin (159), and resistin (160) would be available for routine measurement, these adipocytokines could serve as specific markers for the extent of peripancreatic fat cell necrosis.

The biochemical parameters for predicting the clinical course of acute pancreatitis are currently divided into three (135) categories: 1) markers of pancreatic injury (amylase, lipase); 2) markers of proteolytic activation (trypsinogen pathway); and 3) markers of systemic inflammation (CRP, cytokines). Our intention (158) was to obtain data justifying the addition of a fourth category, *i.e.*, specific markers of fat cell necrosis (adipocytokines).

The role of adiponectin in pancreatitis has not been studied so far, and there exist no precise data on leptin levels during acute necrotizing pancreatitis in humans. In rats, leptin levels were reported to be elevated in both acute ethanol-induced or caerulein-induced pancreatitis (161, 162) and chronic pancreatitis when compared with sham-operated animals. However, no differences between acute and chronic pancreatitis (161) have been observed in these studies. In one single study, leptin levels were measured in patients with edematous pancreatitis and found to be elevated when compared with healthy controls (162). Both in humans with acute edematous pancreatitis and in rats with acute caerulein-induced or ethyl alcohol-induced pancreatitis, plasma leptin levels show a marked increase (161, 162). Both in caerulein-induced (162) and in ischemic (163) pancreatitis, leptin seems to have protective effects on the development of pancreatic damage, probably through activation of the nitric oxide pathway or the limitation of proinflammatory IL-1β release.

Up to now, no data on resistin in the context of acute pancreatitis have been published. Resistin is a member of a new gene family of small cysteine-rich secreted proteins [resistin-like molecule (RELM)α, RELMβ, RELMγ, and resistin] playing an as yet widely uncharacterized role during inflammatory processes (160). In the murine system, lipopolysaccharides (LPS) can increase resistin gene expression *in vivo* and *in vitro* (164). Furthermore, resistin is up-regulated during adipocyte differentiation. Resistin is mainly produced by adipose tissue and monocytes and is secreted from mature adipocytes into the blood stream, where it is detectable in variable amounts by ELISA (165). This observation suggests that resistin acts at sites distant from its synthesis and release (160). Human resistin mRNA expression is higher in abdominal adipose tissue than in sc adipose tissue (166).

Clinical and therapeutical implications: To investigate the potential of the adipocytokines resistin, leptin, and adiponectin as specific markers for the extent of peripancreatic fat cell necrosis and to test for possible associations of these adipocytokines with CT-based pancreatic necrosis scoring systems and potential associations with clinical markers, a prospective study in 23 patients with acute pancreatitis is currently being performed by our clinical research group (158). We could demonstrate that: 1) resistin levels are highly elevated in patients with severe pancreatitis when compared with patients with moderate or mild pancreatitis; 2) resistin levels are correlated with the extent of extrapancreatic necrosis; and 3) resistin positively correlates with systemic CRP levels. A suggested cutoff value above 9.2 ng/ml for systemic resistin provides a highly significant positive predictive value of 91.9% for predicting extrapancreatic necrosis with good sensitivity and specificity. Furthermore, resistin levels determined on d 1 (day of admittance) proved to predict a Schröder score greater than 3 with a positive predictive value of 93.3% (cutoff value, 6.95 ng/ml). Accordingly, d 1 resistin can be regarded as a novel parameter indicating peripancreatic fat cell necrosis, expressed as a Schröder score greater than 3. However, confirmatory and larger studies are needed before transferring these results into routine clinical use.

4. Peritoneal and ascitic fluid. Leptin is detectable in peritoneal fluid of humans. Although peritoneal leptin levels correlate with BMI and body fat content as do serum leptin levels, ascitic fluid leptin levels are higher than serum levels in the absence of spontaneous bacterial peritonitis (167). Further studies have to be performed to investigate whether there is an intraabdominal production of leptin by peritoneal adipocytes.

Clinical and therapeutical implications: It seems reasonable to investigate both locally produced and systemic adipocytokine levels in patients with and without spontaneous bacterial peritonitis because inflammation-induced alteration of local adipocyte function or necrosis of peritoneal adipocytes could release high amounts of adipocytokines that might be used for differential diagnosis of inflammatory *vs.* noninflammatory peritoneal diseases. Interestingly, in mice with experimental bacterial peritonitis, plasma leptin levels increase in response to the induction of TNF-α (168). Moreover, an increase in local adipocytokine production by peritoneal adipocytes in patients with peritoneal tumor spread might have the potential of a tumor marker indicating peritoneal tumor spread. Interestingly, an involvement of leptin in the pathophysiology of Meig's syndrome (ovarian fibroma with ascites and hydrothorax) (169) and pelvic endometriosis (170) has already been suggested.

5. Nonalcoholic steatohepatitis (NASH)/nonalcoholic fatty liver disease (NAFLD). Upon several pathophysiological stimuli, the liver reacts with an increased triglyceride storage and a subsequent necroinflammation. Although there are no site-specific adipose cells within the liver, visceral adipocyte-derived adipocytokines play an important role in NASH/NAFLD. Most recently, this new pathophysiological concept was reviewed extensively (12, 171, 172).

C. Endocrinology

1. Graves' ophthalmopathy. Graves' disease as well as associated thyroid eye disease (Graves' ophthalmopathy) and pretibial dermopathy are caused by autoimmune mechanisms leading to goiter and hyperthyroidism (173, 174). The clinical association between hyperthyroidism, ophthalmopathy, and pretibial dermopathy is suggestive for the pathophysiological role of a common antigen shared by these tissues (175). Thyroid eye disease (176) is now thought to result from the action of thyroid-stimulating autoantibodies directed against the TSH receptor. Genetic (human leukocyte antigen system, molecular mimicry), individual (pregnancy), and environmental (smoking) factors determine a patient's susceptibility to develop the disease. There is increasing evidence that orbital fibroblasts in Graves' disease have unique properties responsible for thyroid eye disease, such as an increased potential to differentiate into mature adipocytes, an exaggerated response to proinflammatory cytokines, an increased secretion of proinflammatory cytokines by themselves, and an increased TGF-β-, IL-1β-, and leucoregulin-induced hyaluronan synthesis (177–182).

After tolerance against the TSH receptor has been lost, autoreactive T cells trigger an immunological inflammatory reaction in tissue compartments expressing the TSH receptor. Subsequently, a Th-1-like cytokine spectrum (183) is released within the orbital space. A wide variety of mediators (183) such as IL-1α, IL-β, IL-2, IL-6, IL-8, IL-10, IL-12, IFN-γ, IGF-I, TGF-β, platelet-derived growth factor, and prostaglandin E_2 are released within the orbital tissue of patients with ophthalmopathy, creating a unique and proinflammatory microenvironment for residing fibroblasts and preadipocytes (173, 184). Whereas IL-6 stimulates TSH receptor gene expression in orbital fibroblasts (185), TNF-α and IFN-γ have inhibitory effects (186). IL-1β induces tissue inhibitor of metalloproteinase-1 in human orbital fibroblasts, thus modulating both the activity of MMP-1 and the composition of extracellular matrix (180).

In Graves' ophthalmopathy, the overabundance of orbital adipose tissue represents a characteristic finding in many patients. Intriguingly, human orbital fibroblasts/preadipocytes can be differentiated into mature adipocytes using appropriate stimulation protocols (187–189). Because both TSH receptor mRNA (190–196) and protein (188, 189, 191, 193, 194, 197–201) are expressed in orbital fibroblasts and adipocytes, these cells can be directly targeted by TSH receptor autoantibodies. Not only the expression but also the functionality of the TSH receptor on orbital adipose cells has been demonstrated in several studies (187, 188, 197, 200). Treatment of orbital preadipocytes with TSH leads to an up-regulation of TSH receptor gene expression (202). This mechanism might explain the clinical observation that hypothyroidism during antithyroidal drug treatment exacerbates ophthalmopathy.

There is increasing evidence for an enhanced adipogenesis in the orbital tissue of patients suffering from Graves' ophthalmopathy (195). Based on this new pathophysiological concept, orbital fibroblasts can undergo an adipogenic differentiation program (187–189, 195). Orbital mature adipocytes resemble the characteristic gene expression profile known from normal adipose tissue with a characteristic expression of adipocyte markers such as PPARγ, adiponectin, leptin, perilipin, IL-6, and, LPL (203). Moreover, orbital adipocytes obtained from patients with Graves' ophthalmopathy have been shown to express even higher levels of leptin (187, 189, 195), adiponectin (195), TSH receptor, and PPARγ (195) than orbital tissues from controls.

The stimulus responsible for the increased *de novo* adipogenesis within the orbital space has not been identified yet. A recent study (203) revealed an up-regulation of sFRP (secreted frizzled related protein-1) in orbital tissues from patients with Graves' ophthalmopathy compared with normal orbital soft tissue. Because sFRP functions as an inhibitor of Wnt signaling, a pathway known to inhibit adipogenesis (57), the up-regulation of sFRP in Graves' ophthalmopathy adipose tissue might explain the phenomenon of an increased *de novo* adipogenesis (195). Moreover, treatment of orbital preadipocytes isolated from patients with Graves' ophthalmopathy with recombinant sFRP induces the expression of the genes for adiponectin, leptin, and TSH receptor (195). After adipogenesis has been induced, the increasing amount of functional TSH receptor protein expressed on the surface of orbital adipocytes makes the adipocyte vulnerable to circulating TSH receptor autoantibodies. It is a well-known clinical feature that patients suffering from Graves' ophthalmopathy show a variable presentation ranging from ocular muscle enlargement to orbital connective/adipose tissue enlargement. Because there is a heterogeneity (204) between orbital fibroblasts and extraocular muscle or dermal fibroblasts (*e.g.*, the expression of the surface glycoprotein Thy-1 or the adipogenic potential), differences in the clinical presentation of Graves' ophthalmopathy might be explained by these observations.

Taken together, the infiltration of the orbital tissue with autoreactive T cells and macrophages leads to the secretion of a wide variety of proinflammatory molecules. This proinflammatory environment seems to trigger the adipogenic conversion of fibroblasts and preadipocytes residing within the orbital space. Along with the adipogenic differentiation, adipocyte-specific genes and the TSH receptor gene are strongly up-regulated. The increasing orbital fat mass leads to the clinical symptom of protrusing ophthalmopathy. The TSH receptor-positive adipose tissue is then being targeted by TSH receptor autoantibodies, most probably leading to an inflammatory transformation and activation of retroorbital adipocytes.

Clinical and therapeutical implications: Treatment of orbital fibroblasts with fenofibrate, a specific activator of PPARα, induces the adipogenic differentiation program and the expression of the genes encoding the adipogenic protein high-mobility group AT-hook 2, leptin, and the TSH receptor (187). PPARγ is also expressed in orbital fibroblasts and mature adipocytes. PPARγ agonists and antagonists can stimulate or decrease adipogenesis, respectively (205). Based on this observation, it has been reported that treatment of type 2 diabetes mellitus with pioglitazone in coexistent Graves' ophthalmopathy worsened thyroid eye disease due to the expansion of the orbital fat content (205). Similarly, rosiglitazone treatment increased adipogenesis exclusively in orbital preadipocytes (198, 204) but not in fibroblasts de-

rived from other tissues. Moreover, rosiglitazone treatment also induced functional TSH receptor expression during the differentiation process of orbital preadipocytes (198). These observations suggest that exacerbation of thyroid eye disease after glitazone treatment is probably caused not only by fluid retention (edema) but also by an increased orbital adipogenesis leading to an expansion of the orbital fat content. Based on this, PPARγ and/or PPARα antagonists might represent future drug targets in Graves' ophthalmopathy. However, there are no additional data or clinical studies up to now supporting that hypothesis.

2. Pretibial dermopathy. Pretibial dermopathy is associated with Graves' disease, and, similar to ophthalmopathy, the pretibial soft tissue containing fibroblasts, preadipocytes, and mature adipocytes is characterized by edema and deposition of hydrophilic glycosaminoglycans. The analysis of the pretibial T cell receptor V gene repertoire showed a restriction of the T cell receptor V usage in both orbital and pretibial tissue in Graves' disease (206). Because preadipocytes and mature adipocytes are localized within pretibial tissue, the TSH receptor expressed locally in pretibial cells (207) might be recognized by oligoclonal T lymphocytes (173, 206). Based on this, pretibial dermopathy is most probably caused by a similar mechanism, as is the case with ophthalmopathy (175).

D. Immunology

1. Perinodal adipocytes and adipocyte-lymph node interaction. It is a well-known anatomical feature that lymph nodes are commonly embedded in adipose tissue. However, the interaction between perinodal adipocytes and lymphoid tissues is poorly understood (208–210). Perinodal adipocytes can respond to signals from activated lymphoid cells (210–212). After activation of a lymph node by LPS or proinflammatory stimuli, lipolysis and glycerol release are increased in perinodal adipocytes (212, 213). It seems interesting to speculate that chronic inflammation and lymph node activation influence adipose tissue function (lipolysis, glycerol release), adipose tissue vascularization, and cytokine receptor expression (214, 215). Adipocytes seem to be involved in local immune responses, and their involvement might explain why most lymph nodes are embedded in adipose tissue (211). In contrast, there are only sparse data indicating that perinodal adipocytes and derived adipocytokines can directly influence lymph node function in a paracrine manner during local inflammatory processes. Adipocytes enclosing lymph nodes might serve to supply immune cells with fuel needed during acute and chronic infection (208, 209).

2. Interaction between fat tissue adipocytes and fat tissue macrophages. An increasing body of evidence supports a correlative and causative relation between insulin resistance or type 2 diabetes mellitus and inflammation (216). Population studies have linked insulin resistance to systemic inflammation (216–218), and obesity is now regarded as a chronic and low-grade inflammatory state (219–221). Moreover, it has become evident that the adipose tissue connects energy metabolism with immune function and host defense (216, 219, 222–224).

Based on this, it seems noteworthy that of 1,300 gene transcripts expressed in white adipose tissue, about 30% encode inflammatory and macrophage-specific genes (225). The reason is that in the context of obesity, the adipose tissue undergoes an inflammatory transformation and becomes infiltrated by significant amounts of macrophages (9). The percentage of macrophages residing within adipose tissue can vary from less than 10% to more than 50% of cells (225, 226).

Xu *et al.* (227) and Weisberg *et al.* (225) performed two groundbreaking studies published in late 2003 and reviewed by Lehrke and Lazar (8) in 2004. These studies reported for the first time that: 1) adipose tissue is infiltrated by significant amounts of macrophages (but not lymphocytes or granulocytes). The number of macrophages is increasing with adipocyte size and the degree of obesity; 2) inflammatory and macrophage genes (*e.g.*, MCP-1) are up-regulated in obesity-related insulin resistance; and 3) proinflammatory cytokines are produced mainly by adipose tissue-homed macrophages rather than by adipocytes.

There exist two basic mechanisms by which macrophages can infiltrate the adipose tissue: first, macrophages can differentiate from bone marrow-derived monocytes that reached the adipose tissue by diapedesis from the systemic circulation; second, macrophages can *trans*-differentiate from local adipose tissue preadipocytes and mesenchymal stem cells. There is evidence from the literature that both mechanisms play a role in inflammatory adipose tissue remodeling.

The molecular basis for a significant diapedesis of blood monocytes into the adipose tissue (225, 226) is provided by the fact that adipocytes secrete a wide variety of chemoattractants that direct monocytes from the circulation into fat stores (219). MCP-1, macrophage migration inhibitory factor, RANTES (CCL5), and macrophage inflammatory protein-1α are secreted from adipose tissue (98, 225, 227–230), and an adipose tissue-derived local supply with M-CSF (101) can support the differentiation and maturation of monocytes into macrophages. A recent study (10) could demonstrate that C-C motif chemokine receptor-2 plays an important role in the recruitment of macrophages to adipose tissue, and this new mechanism was reviewed by Neels and Olefsky (9).

Because adipocytes and macrophages share macrophage-specific antigens and because PPARγ controls both adipocyte and macrophage differentiation and function, it has been suggested that adipocytes and macrophages might not be too different (8). This point of view is supported by a study that demonstrated the *trans*-differentiation of preadipocytes into macrophages acquiring phagocytic activity (231). Based on this observation, macrophages and adipocytes might be interconvertible (8), and local *trans*-differentiation of preadipocytes into mature macrophages can now be regarded as an established process.

Clinical and therapeutical implications: However, the adipose tissue not only regulates its macrophage content but can also control monocyte and macrophage function by the secretion of pro- and antiinflammatory cytokines and adipocytokines such as leptin and adiponectin (219). In this context, it seems important to emphasize that human macrophages express the adiponectin receptor subtypes, AdipoR1 and AdipoR2, and the full-length leptin receptor (232, 233). The cellular

compartment of the adipose tissue is highly variable and can be transformed into a macrophage-containing tissue compartment under certain conditions. The molecular basis for this concept is provided by the fact that adipocytes can secrete a wide panel of proinflammatory mediators and chemoattractants necessary for local *trans*-differentiation and systemic diapedesis of monocytes/macrophages (7, 219, 234). Future work is necessary to demonstrate which conditions and stimuli trigger this inflammatory remodeling of the adipose tissue.

Macrophages resident within adipose tissue might represent a future drug target for diseases that are characterized by an adipose tissue inflammation. A fascinating perspective of adipose tissue monocytes could be the specific transport and release of drugs or gene products into adipose tissue. A future gene therapy approach for the treatment of obesity could be imaginable. Transgenic monocytes carrying specific genes (*e.g.*, lipases or differentiation inhibitors) under the control of an adipocyte-specific promoter could be directed into fat stores where the gene of interest can be activated locally.

3. Adipocytokines, innate immunity, and monocyte/macrophage function. Dendritic cells and macrophages provide a first line of defense against infectious pathogens. Macrophages recognize microbial pathogens by pattern recognition receptors such as toll-like receptors or scavenger receptors. Recognition of foreign microorganisms triggers phagocytosis and the eventual destruction of microorganisms by lysosomal enzymes, reactive oxygen, and nitrogen species. Binding of microbial products like endotoxin stimulates macrophages to release cytokines that influence the innate and, subsequently, the adaptive immune response (235). Adiponectin is an adipocytokine that is highly abundant in human serum, and trimeric, hexameric, and high molecular weight (HMW) isoforms have been described. Mutations in the gene encoding adiponectin can cause impaired multimer formation, lower HMW isoforms in the plasma, or reduced abundance of all adiponectin isoforms owing to a disturbed secretion of adiponectin from the cell (236). Adiponectin exerts immunomodulatory effects and a reduced secretion of the proinflammatory cytokines IL-6, TNF-α, and IFN-γ. Moreover, an enhanced release of IL-10 and IL-1RA in endotoxin-activated monocytes has been described (237–239). The immunosuppressive response is partly explained by reduced NF-κB signaling and ERK1/2 activity. Whereas trimeric adiponectin inhibits NF-κB, hexameric and HMW isoforms of this protein activate NF-κB (240) and may explain induction of IL-6 in monocytes treated with HMW adiponectin. HMW adiponectin reduces phagocytosis of apoptotic cells and IL-8 production in the absence of LPS. In contrast, in LPS-stimulated monocytes, both IL-8 secretion and phagocytosis are stimulated. Therefore, adiponectin cannot be regarded as an antiinflammatory protein in general but modulates innate immunity in an isoform-dependent way.

Besides alterations in cytokine response, the macrophage scavenger receptor A is down-regulated by adiponectin (147). Macrophage scavenger receptor A binds LPS from Gram-negative bacteria and lipoteichoic acid from Gram-positive bacteria and mediates nonopsonin-dependent phagocytosis (241). Uptake of fluorescent microspheres is also impaired in adiponectin-treated macrophages. Suppression was mediated by the complement receptor C1qRp, because anti-C1qRp monoclonal antibody abrogated this effect (147).

Blood monocytes may differentiate into macrophages or dendritic cells. In adiponectin-treated macrophages, LPL abundance and phagocytosis is impaired. Furthermore, reduced proliferation but not viability has been described (147). In monocyte-derived dendritic cells, adiponectin did not influence the allostimulatory capacity. Moreover, adiponectin-treated dendritic cells did not show any changes in the cell surface expression of CD80, CD83, CD86, CD1α, CD11c, CD14, CD40, CD54, CCR6, CCR7, and major histocompatibility complex II, and phagocytic activity was not affected (239). Therefore, adiponectin strongly influences monocytes and macrophages, whereas dendritic cells seem not to be affected by this adipocytokine. Altered cytokine secretion from macrophages may influence the immune response, but the effects of adiponectin on cells of the innate and adaptive immune activation have not been studied in detail. At least levels of circulating adiponectin were shown to be unaltered in animal and human endotoxinemia (242–244).

Leptin belongs to the type I cytokine superfamily, and its functional receptor is expressed in immune cells. In monocytes/macrophages, phagocytosis and the secretion of proinflammatory cytokines, nitric oxide (245), and prostaglandin E_2 are potentiated by leptin (233). Proliferation and the surface expression of early and late activation markers are induced on macrophages by recombinant leptin *in vitro* (246). In neutrophils, leptin exerts antiapoptotic effects and stimulates complement-mediated phagocytosis and chemotaxis (247–249). Furthermore, leptin itself is a potent chemoattractant for these cells (248). Leptin also affects natural killer cell differentiation, proliferation, and activation (250). Leptin does not stimulate naive $CD4^+$ and $CD8^+$ T cells but enhances proliferation and activation of stimulated T cells, further increasing CD69, CD71 (transferrin receptor), and CD25 (α-chain of IL-2 receptor) abundance (251). However, in $CD4^+$ memory T cells, leptin inhibits CD3-induced proliferation and cytokine secretion.

Human leptin deficiency is associated with reduced numbers of circulating $CD4^+$ T cells, impaired T cell proliferation, and reduced secretion of cytokines such as IL-4, IL-10, and IFN-α. Recombinant leptin nearly restores T cell responsiveness to normal levels and increases cytokine secretion (252). In contrast, administration of recombinant leptin to healthy probands did not influence levels of circulating cytokines (253). Therefore, in leptin-sufficient states, a further elevation of circulating leptin does not affect inflammatory markers.

Plasma leptin levels are increased in sepsis survivors (254) and were found to be elevated both in humans during experimental endotoxemia (255) and in TNF-α-injected humans (256). Although most animal studies indicate that leptin-deficient animals are protected from the toxic effects of innate immunity and T cell-mediated inflammation (257), some studies describe an elevated TNF synthesis in leptin deficiency, an enhanced sensitivity to *Listeria* monocytogenes infection, and a higher endotoxin-induced lethality (258).

In summary, these data indicate that physiological levels of leptin are needed to maintain an optimal immune response. Leptin deficiency or leptin resistance as in obese humans may impair innate and adaptive immune cells. Ac-

cordingly, the risk of infection is higher in states of energy deficiency and excess, both associated with adipocytokine dysregulation (259). Depletion of adipose tissue reduces circulating leptin and adiponectin (260), whereas an elevated fat mass is accompanied by high leptin, peripheral leptin resistance, and low adiponectin (224). Both of these adipokines have immunoregulatory functions, and impaired systemic or local levels of these adipokines may account for a disturbed immune function. These findings further support the idea of an important crosstalk between adipose tissue and the immune system.

E. Infectiology

1. Microbial infection of adipose tissue. Little attention has been given to the role of adipocytes as a primary site of microbial infection. However, adipocytes can be infected directly by *Trypanosoma cruzi* with a high efficiency (170). After infection, the intracellular parasites cluster around lipid droplets and affect the expression and secretion of adipocytokines such as adiponectin. During chronic infection, adipocytes may represent a long-term reservoir for parasites. Similarly, *Mycobacterium leprae* survives intracellularly in preadipocytes, and a multiplication occurs during adipocyte differentiation (261). It has been a matter of controversy whether or not the HIV-1 retrovirus can directly infect adipocytes (262). However, it is becoming clear that human adipocytes can be infected by HIV-1 (263). A productive infection of the adipose tissue by HIV-1 at least requires proinflammatory stimulation of the adipose tissue, *e.g.*, by TNF-α or IL-1β (263). Accordingly, future research should address the adipose tissue as a potential reservoir of chronic microbial infections.

F. Hematology

1. The role of bone marrow adipocytes in hematopoiesis and bone homeostasis. During aging, the hematopoietic bone marrow is becoming more and more replaced by adipose tissue, whereas the number of bone-forming osteoblasts decreases (264–266). This kind of remodeling is caused by a switch of bone marrow mesenchymal stem cell commitment from the osteoblast lineage to the adipocyte lineage (266, 267), probably caused by an increased PPARγ_2 expression or activation (264). From one point of view, one could assume that this adipose tissue only functions as a space keeper or as a local energy store. However, because hematopoietically active bone marrow consists of varying amounts of residing preadipocytes and adipocytes, it has long been speculated that adipocytes might act as functional components of bone marrow influencing hematopoiesis in a paracrine manner.

Most importantly in this context, adipocytes and bone marrow stromal cells supporting hematopoiesis develop from the same mesenchymal stem cell (268, 269), and pluripotent stems cells can be isolated from adipose tissue stromal cells (17). Moreover, bone marrow stromal cells have the potential to differentiate into mature adipocytes (269–271). The molecular mechanism behind the commitment of a mesenchymal stem cell toward adipocyte differentiation is only poorly understood but is currently under investigation as a hot topic (269). One important question is whether or not mesenchymal stem cell-derived adipocytes are different from sc or visceral preadipocyte-derived adipocytes. With respect to several metabolic pathways and the expression of adiponectin and leptin, mesenchymal stem cell-derived adipocytes seem to be comparable to preadipocyte-derived mature adipocytes (269). The transcription factor delta-like-1/Pref-1 is expressed in mesenchymal stem cells and inhibits the adipogenic differentiation program (245).

Because adipocytes are the most abundant stromal cell phenotypes in human adult bone marrow, an important supportive function in hematopoiesis is most likely. Adiponectin and leptin are among the most probable and putative adipocytokines to control hematopoiesis (272). Interestingly, adiponectin serum levels were reported to be inversely correlated with red blood cell counts, white blood cell counts, and platelet counts in peripheral blood (272).

Adiponectin is produced by human bone marrow adipocytes in significant amounts, and both adiponectin receptor subtypes AdipoR1 and AdipoR2 are expressed in adipocytes and monocytes (4). Adiponectin inhibits the differentiation of bone marrow preadipocytes in a paracrine manner (273) by induction of COX-2 gene expression and secretion of prostaglandin E (2). Therefore, adiponectin controls the amount of differentiated adipose tissue within bone marrow. Furthermore, this antiinflammatory adipocytokine has been suggested to act directly on hematopoiesis. Adiponectin inhibits the proliferation of myelomonocytic lineage cells. It suppresses colony formation from several colony-forming units, such as CFU-macrophage, CFU-granulocyte-macrophage, and CFU-granulocyte. In addition, it inhibits the proliferation of several myeloid cell lines (238). Recombinant adiponectin also inhibits lymphopoiesis of early lymphocyte precursors via induction of the cyclooxygenase-prostaglandin E_2 pathway (274).

High-affinity leptin receptors are expressed in human mesenchymal stem cells (275). Leptin is secreted by human bone marrow adipocytes, and its expression is inhibited by IL-1β, IL-6, TNF-α, and, IFG-γ (276). Using a coculture system, it could be demonstrated that bone marrow adipocytes support a complete myeloid and lymphoid differentiation from human CD34+ cells (277). Leptin treatment of CD34+ progenitors stimulates the appearance of granulocyte-macrophage colonies (278–280). Leptin stimulates the proliferation of acute myeloid leukemia cells (281) and, in acute promyelocytic leukemia cells, bone marrow adipocyte-derived leptin stimulates cell survival (282). Due to this stimulatory effect, the leptin-leptin receptor system has been suggested to play a role in the pathophysiology of leukemia (283, 284). Additionally, leptin acts synergistically with erythropoietin to stimulate erythroid development (278).

Despite their influence on hematopoiesis, adiponectin and leptin might also regulate bone formation and bone homeostasis because leptin receptors and the specific adiponectin receptors AdipoR1 and AdipoR2 are expressed in bone and primary human osteoblasts (275, 277). Indeed, adiponectin was shown to increase bone mass by suppressing osteoclastogenesis and increasing osteoblastogenesis (285). In detail, adiponectin induces human osteoblast proliferation via the adiponectin/c-jun N-terminal kinase pathway and osteoblast differentiation via the AdipoR/p38 pathway

(286). Similarly, leptin treatment can prevent bone loss by exerting positive effects on osteoblasts and negative effects on osteoclastogenesis (287, 288). Taken together, these data indicate that bone marrow adipocytes provide a specific microenvironment within the bone cavity to regulate bone metabolism/formation and hematopoiesis.

Clinical and therapeutical implications: The local control of adipogenesis and adipocytokine secretion in bone marrow adipocytes might represent a promising drug target in hematology and osteology. Osteoblast activation by adipocytokines could be used for the treatment of osteoporosis and bone diseases. Recombinant adipocytokines might represent future drugs in hematology for lineage-specific stimulation or inhibition of cell growth, differentiation, and proliferation.

Acknowledgments

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