An increase in adipocyte number is a major contributor to the increase in adipose tissue mass that is characteristic of obesity. The identity and regulation of the adipocyte precursor cell (or preadipocyte) and the preadipocyte precursor cell (or progenitor cell) have been intensely studied for many years. In this issue of the JCI, Crossno et al. report that progenitor cells originating from outside the adipose tissue, in particular the bone marrow, can contribute to an increase in adipocyte number (see the related article beginning on page 3220). Their study in mice reveals that treatment with the thiazolidinedione rosiglitazone or exposure to a high-fat diet promotes the trafficking of circulating bone marrow–derived progenitor cells into adipose tissue, where they become multicellular adipocytes. This adds a new and unexpected dimension to this research arena.

Historical perspective
Early investigations noted that the full range of cells common to red bone marrow, including monocytes, reticular cells, lymphocytes, normoblasts, erythroblasts, and basophils, were observed in developing adipose tissue. In particular, a wide range of cell phenotypes common to red bone marrow, including endothelial cell precursors, pericytes, macrophages, immature macrophages, fibroblast-like perivascular reticular cells, and perivascular mesenchymal cells, were among those implicated as the adipocyte precursor cell (1). Adipose tissue and bone marrow–derived mesenchymal cells are similarly characterized by increases in the expression of key adipocyte markers such as fatty acid–binding protein, lipoprotein lipase, PPARγ, and CCAAT/enhancer-binding protein α (C/EBPα) (4, 5). Bone marrow–derived adipocytes also secrete the adipocyte-specific factors leptin and adiponectin, indicating functional similarity between bone marrow–derived and adipose tissue–derived adipocytes (4). Interestingly, clusters of red bone marrow cell types have been observed in developing adipose tissue (6). The number of these cell types was associated temporally and spatially with the development of large clusters of multicellular (comprising many compartments) adipocytes representative of an immature stage of adipocyte development in white adipose tissue. These observations would seem to counter the long-held belief that new adipocytes arise solely from resident preadipocyte progenitors and hint that progenitor cells from tissues outside adipose depots could contribute to the formation of new adipocytes. In support of the latter concept, in this issue

Nonstandard abbreviations used: TZD, thiazolidinedione.

Conflict of interest: The authors have declared that no conflict of interest exists.

Citation for this article: J Clin Invest. 2006;116:3103–3106 (2006). doi:10.1172/JCI30666.
The Journal of Clinical Investigation

of the JCI Crossno et al. (7) provide evidence that bone marrow–derived progenitor cells do indeed contribute to new adipocytes in adipose tissue. The authors exposed GFP–labeled bone marrow–transplanted mice to 2 known inducers of new fat cell formation, either a high-fat diet or treatment with the thiazolidinedione (TZD) rosiglitazone. Subsequent examination demonstrated the presence of GFP+ multilocular adipocytes within adipose tissue that were significantly increased in number by both high-fat feeding and TZD treatment. Furthermore, the GFP+ multilocular adipocytes expressed many genes that are known markers of the adipocyte phenotype, providing additional evidence that the bone marrow–derived progenitor cells had trafficked to adipose tissue where they differentiated into multilocular adipocytes.

TZDs, adipogenesis, and endothelial cells

TZDs are PPARγ ligands currently used in the treatment of type 2 diabetes mellitus. In vitro, TZDs consistently induce adipogenesis, although in many instances the accompanying lipid accretion is minimal (8, 9). TZD treatment in vivo typically increases the number of small multilocular adipocytes and decreases the number of larger adipocytes (10). As a result, adipose tissue undergoes “remodeling,” since clusters of small multilocular adipocytes develop throughout the tissue (10). The morphological results of TZD treatment observed by Crossno et al. (7) are consistent with these previous findings. Similar clusters of multilocular adipocytes were also reported in adipose tissue of mice treated with β3-adrenergic receptor agonists that exert antidiabetic effects in rodents (11). Although transitory in nature, clusters of multilocular adipocytes in developing adipose tissue and those induced by TZDs (10) and β3-adrenergic receptor agonists (11) may share some biochemical characteristics. TZDs also promote mobilization and homing of bone marrow–derived circulatory endothelial progenitor cells to various tissues in the process of endothelial regeneration (12, 13). The demonstration of preadipocyte trafficking from nonresident sources has stimulated these and many other intriguing questions, which will undoubtedly be addressed as mechanisms and regulatory influences on adipose tissue expansion are further defined.

High-fat feeding

Calorie-dense diets, including high-fat diets, increase adipocyte number and size in rodents. In mice fed high-fat diets from birth, increases in fat pad weight were associated with a greater fat cell size through 18 weeks of age, followed by an increase in fat cell number through 52 weeks of age (14). High-fat feeding–induced obesity in adult rodents is also characterized by an increase in fat cell size (7, 15), followed by an increase in fat cell number, which is a
consequence of proliferation of resident preadipocyte progenitors, as demonstrated by increased rates of progenitor cell \(^{14}H\) thymidine incorporation (16). Crossno et al. (7) have shown that trafficking of bone marrow–derived circulating progenitors to adipose tissue represents an additional and novel mechanism of expanding the number of preadipocyte progenitors in response to calorie-dense diets. Future studies will determine the role or contribution of nonresident preadipocyte progenitors in obesity caused by factors other than high-fat feeding.

Adipose tissue depot–dependent traits

A large number of characteristics distinguish adipose tissue locations or depots from each other, including adipocyte number and size, insulin signaling, glucose and lipid metabolism, lipolytic rates, and cytokine expression and secretion (17, 18). Depot-dependent blood flow and innervation density may be the most important depot-dependent traits, since they are associated with adipocyte growth patterns and adipocyte metabolism (17, 18). Subcutaneous adipose tissue and internal (mesenteric) adipose tissue represent extremes in blood flow and innervation density (17). In humans, internal or visceral adipose tissue is associated with the insulin resistance syndrome to a greater degree than is subcutaneous adipose tissue (18). The abundance of non-adipocyte cell types and their differentiation potential are very depot dependent in rat adipose tissue (19). These studies indicate that adipose tissue–derived stromal vascular cells (progenitor cells) give rise to osteoblasts, endothelial cells, and hematopoietic cells, depending on culture conditions and depot (19). In particular, the number of resident bone progenitor cells was highest in white adipose tissue and lowest in brown adipose tissue (19). Could there be a depot-dependent influence on nonresident progenitor cell pools as well? The results presented by Crossno et al. (7) further hint that this may be the case, as they demonstrated that bone marrow–derived adipocyte progenitors (nonresident) were distributed as large clusters in white adipose tissue (omental), but as single cells in brown (interscapular) adipose tissue.

Adipocyte development and angiogenesis

It is important to consider adipocyte development in relation to vasculogenesis and angiogenesis (Figure 1), since adipocyte development (adipogenesis) and vasculogenesis/angiogenesis are reciprocally regulated events (20). For instance, vasculogenesis and angiogenesis either precede or are coincidental with adipogenesis during fetal adipose tissue development (20). There are many other lines of evidence of developmental or autocrine/paracrine relationships between capillaries/endothelial cells and preadipocytes (Figure 1; ref. 20).

Implanting murine preadipocytes in a dorsal skin–fold chamber has been shown to induce angiogenesis and formation of fat pads (21). The induced blood vessels subsequently developed and remodeled into a mature vasculature associated with differentiated adipocytes (21). The vasculature development and remodeling demonstrated by Fukumura et al. (21) were virtually identical to those observed during adipose tissue development in vivo (20). Implantation of murine preadipocytes transduced with a recombinant adenovirus encoding a PPARy–dominant-negative mutant receptor in a dorsal skin–fold chamber markedly reduced adipocyte differentiation but also markedly reduced angiogenesis compared with the effects of implanting preadipocytes transduced with a mock adenovirus (21). Furthermore, blocking angiogenesis with an antibody to VEGFR-2 (a transducer of the major signals of angiogenesis via tyrosine kinase activity) reduced angiogenesis and inhibited adipocyte differentiation (21). Conversely, neovascularization induced with injections of Matrigel supplemented with basic FGF recruited and induced migration of preadipocyte progenitors from adjacent connective tissue, which ultimately resulted in the formation of a fat pad at the injection site (22).

Related studies have demonstrated that adipose tissue can be effectively regulated by its vasculature (23). For instance, treatment with angiogenesis inhibitors selectively inhibits adipose tissue growth and prevents high-fat feeding–induced and genetic obesity in mice (23). This and other studies indicate that vascular stability, i.e., vascular maturity, per se can dictate adipocyte development and adiposity.

Considering the reciprocal relationship between blood vessel and adipocyte development and the intriguing results presented by Crossno et al. (7) provokes many additional questions: What is the relationship, if any, between nonresident bone marrow–derived preadipocyte progenitors and vasculogenesis/angiogenesis? Is there a common mechanism(s) governing the development of new blood vessels associated with adipocyte development? Could the angiogenic potential and angiogenic capacity of preadipocytes be controlled by different signals? Do bone marrow–derived progenitors home in on newly formed adipose tissue vasculature? Or, conversely, can nonresident (bone marrow–derived) preadipocyte progenitors induce adipose tissue neovascularization? What is the role of preadipocytes in the development and maintenance of the adipose tissue vasculature? Finally, the study by Crossno et al. (7) has ushered in terminology distinguishing nonresident and resident preadipocyte progenitors and has clearly expanded the possibilities in the search for the preadipocyte progenitor cell.

Address correspondence to: Gary J. Hausman, USDA-ARS, South Atlantic Area, PO Box 5677, 950 College Station Road, Athens, Georgia 30604-5677, USA. Phone: (706) 583-8275; Fax: (706) 542-0399; E-mail: ghausman@saa.ars.usda.gov.

Selectins revisited: the emerging role of platelets in inflammatory lung disease

Wolfgang M. Kuebler
Institute of Physiology, Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, and Department of Anesthesiology, German Heart Institute Berlin, Berlin, Germany.

Neutrophil infiltration into the lung is considered a crucial step in the pathogenesis of acute lung injury, yet data on the underlying mechanisms have been ambiguous: although selectin-mediated leukocyte rolling is absent in lung capillaries, therapeutic strategies targeted at selectin-mediated cell–cell interactions yield partial protection. The study by Zarbock and coworkers in this issue of the JCI solves this apparent contradiction by identifying selectin-mediated platelet-neutrophil interaction as a critical step in the mutual activation of leukocytes and endothelial cells (see the related article beginning on page 3211). The emerging role of platelets may be of broad clinical relevance in lung inflammatory disorders, including asthma, chronic obstructive pulmonary disease, and cystic fibrosis.

Forty years after its first clinical description, acute lung injury (ALI) and its most severe form, the acute respiratory distress syndrome (ARDS), remain life-threatening conditions with reported age-adjusted incidences as high as 86.2 per 100,000 person-years and in-hospital mortality rates ranging between 31% and 38% (1, 2). The pathogenesis of ALI and ARDS is closely linked to intrapulmonary and systemic inflammatory responses. Neutrophils in particular have been implicated in the onset of both diseases based on the rapid accumulation of these cells observed in histologic lung specimens and bronchoalveolar lavage fluid from affected patients (3, 4). In many experimental models, a role for neutrophils in lung injury was supported by partial protection against injury following neutrophil depletion. Yet the causative role of neutrophils in ALI or ARDS has also been challenged by the clinical observation that even profound neutropenia does not protect patients from ALI and ARDS (5). Although the question of how many neutrophils are required to induce tissue injury remains unanswered, the latter observation suggests that neutrophil accumulation is not imperative for the onset of these diseases and that other inflammatory cells may be involved and compensate for neutropenia.

**Neutrophil kinetics in the lung**

In principle, neutrophil accumulation and subsequent tissue injury are the result of a multistep process comprising the initial tethering of circulating blood cells to the vessel wall and their subsequent rolling along the wall, followed by firm adherence and finally extravasation. This sequence of events is mediated by consecutive involvement of different families of adhesion molecules; while neutrophil rolling is mediated by selectins interacting with their respective glycoprotein counterligands, firm adhesion results from the interaction of neutrophil β2-integrins with ICAMs expressed on the endothelium. In the systemic circulation, this sequence of events is predominantly confined to the venular compartment. In contrast, the prevalent site of leukocyte accumulation and emigration in the lung is the pulmonary capillary bed (6, 7). In lung capillaries, neutrophils do not roll but are temporarily retained at distinct sites of the alveolar capillary network for periods ranging from less than 1 second to more than 20 minutes (8). This phenomenon has been attributed to mechanical retention of circulating neutrophils in the narrow segments of the alveolar capillary network. Following mechanical arrest, the propelling blood flow slowly deforms neutrophils into an elongated shape, ultimately allowing them to continue their passage (9). In accordance with this notion, excessive accumulation of neutrophils in lung capillaries in systemic or pulmonary inflammation has been attributed to increased neutrophil stiffening by polymerization of monomeric to filamentous actin and subsequent firm adhesion to the endothelium via β2-integrins (10).