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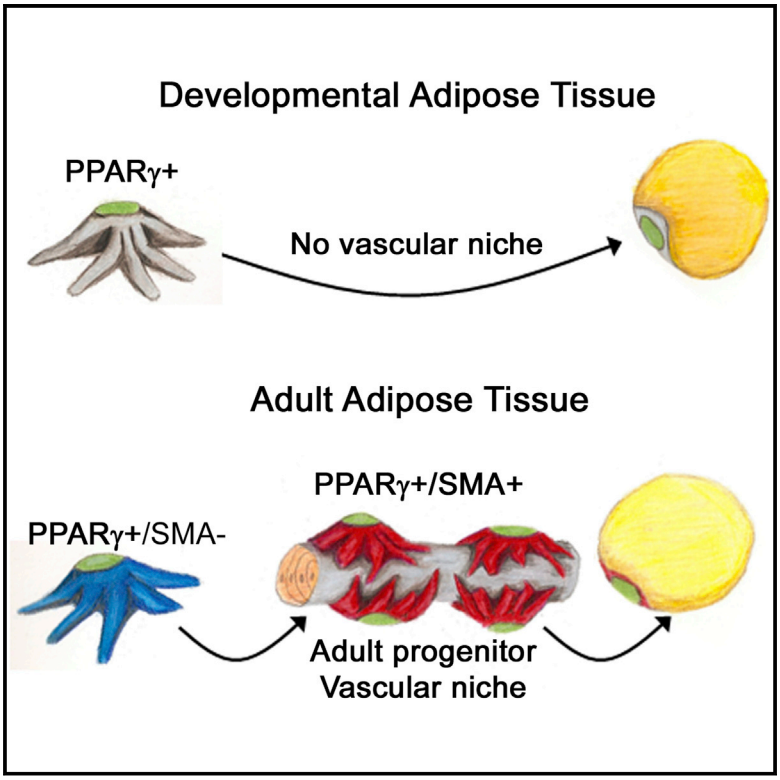
Independent Stem Cell Lineages Regulate Adipose Organogenesis and Adipose Homeostasis

Graphical Abstract



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In Brief

Adipose tissue development and progenitor cell specification are unclear. Jiang et al. identify two types of adipose progenitor cells, developmental and adult, that participate in organogenesis and homeostasis, respectively. Only adult progenitors fate-map from a smooth muscle actin mural lineage and are specified during embryogenesis, highlighting a potential therapeutic target for childhood and adult obesity.

Highlights

PPARγ+ progenitors are essential for adipose tissue organogenesis and homeostasis

Developmental and adult adipose progenitors show diverse features

Adult, but not developmental, adipocytes fate-map from a mural cell lineage

Adult progenitors are embryonically specified before developmental progenitors

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Independent Stem Cell Lineages Regulate Adipose Organogenesis and Adipose Homeostasis

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SUMMARY

Adipose tissues have striking plasticity, highlighted by childhood and adult obesity. Using adipose lineage analyses, smooth muscle actin (SMA)-mural cell-fate mapping, and conditional PPARγ deletion to block adipocyte differentiation, we find two phases of adipocyte generation that emanate from two independent adipose progenitor compartments: developmental and adult. These two compartments are sequentially required for organ formation and maintenance. Although both developmental and adult progenitors are specified during the developmental period and express PPARγ, they have distinct microanatomical, functional, morphogenetic, and molecular profiles. Furthermore, the two compartments derive from different lineages; whereas adult adipose progenitors fate-map from an SMA+ mural lineage, developmental progenitors do not. Remarkably, the adult progenitor compartment appears to be specified earlier than the developmental cells and then enters the already developmentally formed adipose depots. Thus, two distinct cell compartments control adipose organ development and organ homeostasis, which may provide a discrete therapeutic target for childhood and adult obesity.

INTRODUCTION

Adipose depots develop in utero and during childhood (Birsoy et al., 2011; Tang et al., 2008). Once formed, white adipocytes store triglycerides and produce signals that regulate systemic metabolism (Rosen and Spiegelman, 2006; Spiegelman and Flier, 2001). During childhood and adult life, adipose depots protect against trauma and the cold and control a variety of processes such as thermoregulation and appetite (Rousseau et al., 2003). Adipose depots also appear to have adult-specific roles such as in fecundity, reproduction, and lifespan control (Hossain et al., 2007; Rosen and Spiegelman, 2006; Schwimmer and Haim, 2009; Spiegelman and Flier, 2001). Yet whether the stem cells that generate the two types of adipocytes, childhood and adult, are related is unknown (Prins and O'Rahilly, 1997). What appears clear is that forming and maintaining a relatively constant pool of adipocytes is essential for health; an excess (obesity) or deficit (lipodystrophy) of adipose tissue leads to metabolic dysfunction (Ailhaud et al., 1992; Gesta et al., 2007). Several lines of evidence, including human studies, indicate that new adipocyte formation is a key aspect of adult homeostatic balance and is required for maintenance and turnover throughout life (Faust et al., 1978; Johnson and Hirsch, 1972; Spalding et al., 2008). Further, obesogenic and other external stimuli appear to change the adipose turnover rate, and recent studies support the notion that such cues trigger formation of new adipocytes, possibly from an adipose stem compartment (Daniels, 2006; Hossain et al., 2007; Kopelman, 2000).

Tissue development and homeostasis often require a steady replenishment of cells from stem or progenitor sources (Weissman, 2000). These cells typically reside in a niche, a critical specialized microenvironment that regulates transitions of stem cells between quiescence, proliferation, and differentiation (Li and Clevers, 2010). Using a lineage marking system termed AdipoTrak (Tang et al., 2008), we recently began to identify and characterize a population of adipose progenitors that appear to have stem function and express PPARγ, a master regulator of adipocyte differentiation (Chawla et al., 1994; Tontonoz et al., 1994). For example, AdipoTrak-marked cells exhibit many canonical stem properties, such as their ability to self-renew, proliferate, and differentiate into adipocytes. In AdipoTrak, we recombined the tet-transactivator (tTA; "Dox Off" system) into the endogenous PPARγ locus (*PPARγ^{tTA}*) and combined this with complementary reporter systems (e.g., *TRE-H2B-GFP; TRE-Cre, R26R^{lacZ}*). Although the system has limited ability to mirror the dynamic expression of endogenous PPARγ, largely due to the long perdurance of *TRE-H2B-GFP* (Kanda et al., 1998) and the indelible marking of *R26R^{lacZ}*, AdipoTrak shows predominant adipose-restricted expression and can be effectively suppressed by doxycycline (Tang et al., 2008). Using these tools, we found that some AdipoTrak-marked cells resemble a subset of mural cells and localize to the perivascular region in established depots, which we postulated serves as an adipose progenitor cell niche (Tang et al., 2008). Mural cells, also termed pericytes or vascular smooth muscle cells denoting their expression of smooth muscle actin (SMA), reside at the vascular/periendothelial

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