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Table 1. BrdU Counts in Adipose Tissue of C57/BL6 Mice.

Sex	Age	Days BrdU	Total Nuclei Counted	Perilipin$^+$ Cells Labeled with BrdU	%Perilipin$^+$ Cells Labeled with BrdU Per Day	Total Nuclei Counted	C/EBPα^+ Cells Labeled with BrdU	C/EBPα^+ Cells Labeled with BrdU Per Day
Female	6 weeks	1	1756	0.5%	0.5%	n/d	n/d	n/d
Female	6 weeks	1	1512	0.2%	0.2%	n/d	n/d	n/d
Female	6 weeks	1	2921	0.8%	0.8%	n/d	n/d	n/d
Female	6 weeks	1	1007	0.2%	0.2%	n/d	n/d	n/d
Female	6 weeks	1	1190	0.6%	0.6%	n/d	n/d	n/d
Male	6 weeks	1	2438	0.8%	0.8%	n/d	n/d	n/d
Male	6 weeks	1	1433	0.7%	0.7%	n/d	n/d	n/d
Female	6 weeks	3	1862	1.9%	0.6%	n/d	n/d	n/d
Female	6 weeks	3	1580	1.6%	0.5%	n/d	n/d	n/d
Female	6 weeks	3	782	1.4%	0.5%	n/d	n/d	n/d
Female	6 weeks	3	1478	2.0%	0.7%	n/d	n/d	n/d
Female	6 weeks	3	2283	1.4%	0.5%	n/d	n/d	n/d
Male	6 weeks	3	1558	1.0%	0.3%	n/d	n/d	n/d
Male	6 weeks	3	1201	2.0%	0.7%	n/d	n/d	n/d
Female	6 weeks	5	1073	3.0%	0.6%	n/d	n/d	n/d
Female	6 weeks	5	2235	2.4%	0.5%	n/d	n/d	n/d
Female	6 weeks	5	1809	2.0%	0.4%	n/d	n/d	n/d
Female	6 weeks	5	1709	3.4%	0.7%	n/d	n/d	n/d
Male	6 weeks	5	2304	2.0%	0.4%	n/d	n/d	n/d
Male	6 weeks	5	2528	2.3%	0.5%	n/d	n/d	n/d
Female	6 weeks	7	915	7.5%	1.1%	n/d	n/d	n/d
Female	6 weeks	7	1379	5.3%	0.8%	n/d	n/d	n/d
Female	6 weeks	7	2454	4.4%	0.6%	n/d	n/d	n/d
Female	6 weeks	7	1034	7.0%	1.0%	n/d	n/d	n/d
Female	6 weeks	7	779	8.2%	1.2%	n/d	n/d	n/d
Female	6 weeks	7	1489	2.4%	0.3%	n/d	n/d	n/d
Male	6 weeks	7	1053	3.0%	0.4%	n/d	n/d	n/d
Male	6 weeks	7	1051	6.0%	0.9%	n/d	n/d	n/d
Male	6 weeks	7	1502	4.0%	0.6%	n/d	n/d	n/d
Female	6 weeks	10	2622	8.1%	0.8%	n/d	n/d	n/d
Female	6 weeks	10	1719	8.0%	0.8%	n/d	n/d	n/d
Female	6 weeks	10	1160	5.8%	0.6%	n/d	n/d	n/d
Female	6 weeks	10	1035	6.4%	0.6%	n/d	n/d	n/d
Female	6 weeks	10	1258	8.8%	0.9%	n/d	n/d	n/d
Male	6 weeks	10	1238	6.5%	0.7%	n/d	n/d	n/d
Male	6 weeks	10	1925	8.5%	0.9%	n/d	n/d	n/d
Male	6 weeks	1	n/d	n/d	n/d	1388	2.1%	2.1%

Male	6 weeks	3	n/d	n/d	n/d	1100	4.5%	1.5%
Male	6 weeks	5	n/d	n/d	n/d	1677	8.0%	1.6%
Male	6 weeks	7	n/d	n/d	n/d	1710	14.0%	2.0%
Summary			57272		0.63%	5875		1.78%

Table 2. Ki67 Counts in C/EBPα-Labeled Adipose Tissue of C57/BL6 Mice.				
Sex	**Age**	**Total Nuclei Counted**	**C/EBPα^{+} Cells Labeled with Ki67**	**% C/EBPα^{+} Cells of Total Nuclei**
Female	6 weeks	1169	4.0%	40.5%
Female	6 weeks	1792	3.3%	51.5%
Female	6 weeks	1097	4.0%	54.3%
Male	6 weeks	737	3.4%	44.0%
Male	6 weeks	1834	4.2%	68.0%
Male	6 weeks	1012	6.6%	43.5%
Female	14 weeks	964	4.8%	45.6%
Female	14 weeks	1472	4.4%	44.3%
Female	14 weeks	1092	3.6%	56.7%
Male	14 weeks	1282	4.5%	26.0%
Male	14 weeks	1107	2.0%	48.7%
Male	14 weeks	580	6.1%	39.5%
Male	14 weeks	430	4.7%	58.8%
Male	14 weeks	517	5.8%	56.9%
Male	14 weeks	436	5.6%	61.4%
Male	30 weeks	700	11.2%	35.9%
Male	30 weeks	771	9.3%	60.3%
Male	30 weeks	648	3.1%	54.2%
Summary		17640	5.0%	49.4%

Table 3 Ki67 Counts in Adipose Tissue of C57/BL6 Mice by Confocal Microscope						
Sex	**Age**	**Total %Ki67**	**Total nuclei counted**	**%CD31 cells labeled with Ki67**	**%Ki67+, CD31- within Perilipin populati on**	**%Ki67+ of unknown cell type**
Female	6 weeks	4.8%	1311	0.9%	2.3%	1.5%
Male	6 weeks	4.1%	1390	1.2%	1.4%	1.4%
Female	14 weeks	3.6%	977	0.2%	1.6%	1.8%
Summary		4.2%	3678	0.8%	1.8%	1.5%
Sex	**Age**	**Total %Ki67**	**Total nuclei counted**	**%Mac1 cells labeled with Ki67**		
Female	6 weeks	3%	856	0.6%		
Female	14 weeks	3.4%	960	1.8%		
Summary		3.2%	1816	0.7%		

Table 4. Ki67 Counts in Perilipin-Labeled Adipose Tissue of C57/BL6 Mice.

Sex	Age	Total Nuclei Counted	Ki67+ cells within Perilipin population
Female	6 weeks	1578	2.2%
Female	6 weeks	1024	2.3%
Female	6 weeks	2311	1.3%
Male	6 weeks	1690	2.5%
Male	6 weeks	1267	1.1%
Male	6 weeks	1536	2.4%
Female	14 weeks	1035	2.0%
Female	14 weeks	1383	2.5%
Female	14 weeks	1613	0.8%
Male	14 weeks	1783	1.9%
Male	14 weeks	1271	1.8%
Male	14 weeks	1136	1.0%
Male	14 weeks	1385	1.8%
Male	30 weeks	1567	1.9%
Male	30 weeks	970	1.4%
Male	30 weeks	1486	1.9%
Male	30 weeks	1579	1.4%
Male	30 weeks	384	1.6%
Male	30 weeks	403	1.7%
Summary		25401	1.8%

Table 5. Statistical Analysis of Wildtype Cell Cycle Counts.

Source of Data	Sex	Age	Days BrdU	Adipocyte Stain	Cell Cycle Stain	Average	Standard Deviation
Table 1	Female	6 weeks	n/a	Perilipin	Ki67	2.0%	0.5%
Table 1	Female	14 weeks	n/a	Perilipin	Ki67	1.8%	0.9%
Table 1	Male	6 weeks	n/a	Perilipin	Ki67	2.0%	0.8%
Table 1	Male	14 weeks	n/a	Perilipin	Ki67	1.6%	0.4%
Table 1	Male	30 weeks	n/a	Perilipin	Ki67	1.7%	0.2%
Table 1	Mixed	6 weeks	n/a	Perilipin	Ki67	2.0%	0.7%
Table 1	Mixed	14 weeks	n/a	Perilipin	Ki67	1.7%	0.6%
Table 2	Female	6 weeks	n/a	C/EBPα	Ki67	3.8%	0.4%
Table 2	Female	14 weeks	n/a	C/EBPα	Ki67	4.3%	0.6%
Table 2	Male	6 weeks	n/a	C/EBPα	Ki67	4.7%	1.7%
Table 2	Male	14 weeks	n/a	C/EBPα	Ki67	4.8%	1.5%
Table 2	Male	30 weeks	n/a	C/EBPα	Ki67	7.9%	4.2%
Table 2	Mixed	6 weeks	n/a	C/EBPα	Ki67	4.2%	1.2%
Table 2	Mixed	14 weeks	n/a	C/EBPα	Ki67	4.6%	1.2%
Table 3	Female	6 weeks	1	Perilipin	BrdU	0.5%	0.3%
Table 3	Female	6 weeks	3	Perilipin	BrdU	1.7%	0.3%
Table 3	Female	6 weeks	5	Perilipin	BrdU	2.7%	0.6%
Table 3	Female	6 weeks	7	Perilipin	BrdU	5.8%	2.2%
Table 3	Female	6 weeks	10	Perilipin	BrdU	7.4%	1.3%
Table 3	Male	6 weeks	1	Perilipin	BrdU	0.7%	0.1%
Table 3	Male	6 weeks	3	Perilipin	BrdU	1.5%	0.7%
Table 3	Male	6 weeks	5	Perilipin	BrdU	2.2%	0.2%
Table 3	Male	6 weeks	7	Perilipin	BrdU	4.3%	1.5%
Table 3	Male	6 weeks	10	Perilipin	BrdU	7.5%	1.4%
Table 3	Female	6 weeks	Per Day	Perilipin	BrdU	0.6%	0.2%
Table 3	Male	6 weeks	Per Day	Perilipin	BrdU	0.6%	0.2%

Table 6. Pairwise Statistical Analysis of P-values of Ki67 Counts in Adipose Tissue of C57/BL6 Mice of Various Ages.

Fat Stain Used	Age	6 weeks	14 weeks	30 weeks
Perilipin	**6 weeks**	-	0.4075	0.2669
Perilipin	**14 weeks**		-	0.9033
Perilipin	**30 weeks**			-
C/EBPα	**6 weeks**	-	0.5741	0.2712
C/EBPα	**14 weeks**		-	0.3108
C/EBPα	**30 weeks**			-

Table 7. Ki67 Counts in Adipose Tissue of C57/BL6 OB/OB and DIO Mice.

Sex	Genotype	Age	Total Nuclei Counted	C/EBPα^{+} Cells Labeled with Ki67	% C/EBPα^{+} Cells of Total Nuclei
Female	OB/OB	14 weeks	606	10.9%	34.8%
Female	OB/OB	14 weeks	395	7.0%	32.2%
Female	OB/OB	14 weeks	338	3.7%	39.9%
Male	OB/OB	14 weeks	604	7.5%	43.9%
Male	OB/OB	14 weeks	570	6.9%	50.7%
Male	OB/OB	14 weeks	389	7.8%	39.3%
				C/EBPα^{+} Cells Labeled with Ki67 in Perilipin population	**Total %Ki67**
Female	OB/OB	14weeks	330	10.4%	13.3%
Female	OB/OB	6weeks	565	1.6%	2.3%
Female	OB/OB	6weeks	655	2.6%	3.5%
Female	OB/OB	6weeks	556	3.2%	4.4%
Male	DIO	14 weeks	823	2.7%	3.7%
Male	DIO	14 weeks	347	5.7%	6%
Male	DIO	14 weeks	577	2.4%	2.4%
Summary	DIO	14weeks	1747	3.6%	4%

Table 8. BrdU Counts in Adipose Tissue of C57/BL6 OB/OB Mice Following 5 days of BrdU injection.

Genotype	Sex	Age	Total Nuclei Counted	C/EBPα$^+$ Cells Labeled with BrdU	% C/EBPα$^+$ Cells of Total Nuclei
Wildtype	Female	14 weeks	628	5.1%	62.9%
Wildtype	Female	14 weeks	742	2.7%	55.8%
Wildtype	Female	14 weeks	1028	2.4%	59.7%
Wildtype	Male	14 weeks	653	1.7%	44.1%
Wildtype	Male	14 weeks	495	2.4%	51.7%
OB/OB	Female	14 weeks	357	6.2%	49.9%
OB/OB	Female	14 weeks	333	6.9%	52.6%
OB/OB	Female	14 weeks	628	9.2%	42.4%
OB/OB	Male	14 weeks	466	12.4%	46.8%
OB/OB	Male	14 weeks	397	11.0%	59.7%
OB/OB	Male	14 weeks	285	12.5%	44.9%

Table 9. Statistical Comparison of Wildtype and OB/OB Cell Cycle Counts.

Source of Data	Genotype	Sex	Age	Days BrdU	Adipocyte Stain	Cell Cycle Stain	Average	Standard Deviation	p-valu
Table 1	Wildtype	Female	6 weeks	n/a	C/EBPα	Ki67	3.7%	0.5%	
Table 1	Wildtype	Male	6 weeks	n/a	C/EBPα	Ki67	4.7%	1.7%	0.429
Table 1	Wildtype	Female	14 weeks	n/a	C/EBPα	Ki67	4.2%	0.7%	
Table 1	Wildtype	Male	14 weeks	n/a	C/EBPα	Ki67	4.8%	1.5%	0.478
Table 4	Wildtype	Female	14 weeks	5	C/EBPα	BrdU	3.4%	1.5%	
Table 4	Wildtype	Male	14 weeks	5	C/EBPα	BrdU	2.1%	0.5%	0.255
Table 1	Wildtype	Mixed	6 weeks	n/a	C/EBPα	Ki67	4.2%	1.2%	
Table 1	Wildtype	Mixed	14 weeks	n/a	C/EBPα	Ki67	4.6%	1.2%	0.574
Table 3	OB/OB	Female	14 weeks	n/a	C/EBPα	Ki67	7.2%	3.6%	
Table 3	OB/OB	Male	14 weeks	n/a	C/EBPα	Ki67	7.4%	0.5%	0.932
Table 1	Wildtype	Mixed	14 weeks	n/a	C/EBPα	Ki67	4.6%	1.2%	
Table 3	OB/OB	Mixed	14 weeks	n/a	C/EBPα	Ki67	7.3%	2.3%	0.033
Table 4	OB/OB	Female	14 weeks	5	C/EBPα	BrdU	7.4%	1.6%	
Table 4	OB/OB	Male	14 weeks	5	C/EBPα	BrdU	12.0%	0.9%	0.020
Table 4	Wildtype	Mixed	14 weeks	5	C/EBPα	BrdU	2.9%	1.3%	
Table 4	OB/OB	Mixed	14 weeks	5	C/EBPα	BrdU	9.7%	2.7%	0.000

Table 10. BrdU Counts in Perilipin-Labeled Adipose Tissue of 6 weeks old pregnant C57/BL6 Mice.

Day BrdU	Time point after vaginal plug detection	Total Nuclei Counted	Perilipin+ Cells Labeled with BrdU
1	E0.5	914	0.5%
1	E0.5	905	0.8%
1	E0.5	751	3.3%
1	E0.5	500	2.4%
3	E2.5	357	0.8%
3	E2.5	461	1.5%
3	E2.5	725	5.5%
3	E2.5	419	2.3%
5	E4.5	586	3.5%
5	E4.5	1321	5.6%
7	E6.5	393	7%
7	E6.5	904	6%
1	E8.5	425	3%
1	E8.5	1170	3%
1	E8.5	448	7%
10	E9.5	671	11.9%
10	E9.5	799	10.5%
10	E9.5	1067	7%
3	E10.5	1726	3%
3	E10.5	1095	2%
3	E10.5	545	1.1%
7	E14.5	1002	1%
7	E14.5	1492	4%
7	E14.5	1282	2.1%
Summary		19958	

Table 11. Ki67 Counts in Perilipin-Labeled Adipose Tissue of 6 weeks old pregnant C57/BL6 Mice.

Female	Time point after vaginal plug detection	Total Nuclei Counted	Perilipin+ Cells Labeled with Ki67
	E0.5	947	3.3%
	E0.5	882	6.2%
	E0.5	788	1.4%
	E2.5	1340	1.7%
	E2.5	1189	8%
	E2.5	911	1.4%
	E4.5	1359	4.7%
	E4.5	945	8.8%
	E6.5	1530	5.3%
	E6.5	1321	4.2%
	E8.5	661	3%
	E8.5	738	5%
	E8.5	1257	2.5%
	E9.5	1068	3.9%
	E9.5	1022	5%
	E10.5	1687	3.8%
	E10.5	1436	3.6%
	E10.5	673	2.8%
	E12.5	1065	2.1%
	E12.5	1551	1.1%
	E14.5	2088	2.2%
	E14.5	746	2.5%
Summary		24133	3.5%

Sex	Group	Days BrdU	Total Nuclei Counted	Perilipin^{+} Cells Labeled with BrdU Operated side	Total nuclei counted	Perilipin^{+} Cells Labeled with BrdU Not Operated side
Female	Lipectomy	7	1248	8.1%	1391	2.2%
Female	Lipectomy	7	1083	14%	1267	2.9%
Female	Lipectomy	7	1109	7.4%	1087	2.5%
Female	Lipectomy	7	908	8.3%	1343	8.8%
Female	Lipectomy	7	322	17%	1247	5.9%
Male	Lipectomy	7	1542	10.6%	1339	4.1%
Male	Sham	7	1021	10.9%	982	3.6%
Female	Sham	7	776	1.9%	834	3.7%
Female	Sham	7	842	1.6%	734	3.5%

Table 13. Ki67 Counts in Human Adipose Tissue				
Sex	**Total Nuclei Counted**	**C/EBPα$^+$ Cells Labeled with Ki67 within Perilipin population**	**C/EBPα$^+$ of Total Nuclei within Perilipin population**	**% Ki67$^+$ of Total Nuclei**
Female	575	0.4%	50.5%	0.9%
Female	489	1.0%	45.6%	1.4%
Female	608	0.9%	52.9%	1.0%
Average		0.8%	49.7%	1.1%
Standard Deviation		0.3%	3.7%	0.3%

Table 14. Purity of adipocytes in floating fraction of fat embedded in collagen.

Fat Stain Used	**Total Nuclei Counted**	**% C/EBPα-Positive Cells Labeled with Mature Fat Marker**
BODIPY	132	86.2%
BODIPY	57	96.3%
BODIPY	73	89.5%
Perilipin	112	76.5%
Perilipin	42	100.0%
Total	416	87.9%
Standard Deviation		9.2%

Table 15. AP2-CreER;R26R Lineage Analysis of Adipocytes.				
Experiment	**Genotype**	**Sex**	**Average % of Tissue Pixels Labeled with LacZ**	**Standard Deviation**
Pulse	AP2-CreER;R26R	Female	46.7%	13.0%
Pulse	AP2-CreER;R26R	Female	31.8%	9.1%
Pulse	AP2-CreER;R26R	Female	30.0%	4.2%
Pulse	AP2-CreER;R26R	Female	46.3%	8.3%
Pulse	AP2-CreER;R26R	Male	45.1%	6.7%
Total Pulse			40.0%	8.3%
Chase	AP2-CreER;R26R	Female	44.3%	9.0%
Chase	AP2-CreER;R26R	Female	44.6%	12.5%
Chase	AP2-CreER;R26R	Female	39.1%	14.2%
Chase	AP2-CreER;R26R	Male	40.3%	9.2%
Chase	AP2-CreER;R26R	Male	43.2%	5.5%
Total Chase			42.3%	2.5%
Positive	Rosa-Lacz (Positive)	Female	48.4%	9.5%
Positive	Rosa-Lacz (Positive)	Female	46.9%	7.7%
Positive	Rosa-Lacz (Positive)	Female	48.0%	17.4%
Positive	Rosa-Lacz (Positive)	Female	40.0%	5.7%
Positive	Rosa-Lacz (Positive)	Female	43.6%	4.3%
Total Positive			45.4%	10.3%
Negative	AP2-CreER (Negative)	Female	1.9%	0.7%
Negative	AP2-CreER (Negative)	Female	2.8%	1.2%
Negative	AP2-CreER (Negative)	Female	9.2%	4.5%
Negative	AP2-CreER (Negative)	Female	5.1%	1.8%
Total Negative			4.7%	3.6%

Table 16. Pulse-Chase of AP2-CreER;R26R SV fraction *in vitro*.				
Condition	**Genotype**	**Total Nuclei Counted**	**% LacZ$^+$ of Total Nuclei**	**SD**
Pulse	Rosa-LacZ (Positive)	482	87.2%	10.1%
Pulse	AP2-CreER (Negative)	2354	1.2%	1.1%
Pulse	AP2-CreER;R26R	2338	2.1%	1.8%
Pulse	AP2-CreER;R26R	2873	1.9%	1.1%
Pulse	AP2-CreER;R26R	2129	1.7%	1.3%
Total Pulse	**AP2-CreER;R26R**	**7340**	**1.9%**	**1.4%**
Chase	Rosa-LacZ (Positive)	1482	81.4%	8.1%
Chase	AP2-CreER (Negative)	1942	0.3%	0.5%
Chase	AP2-CreER;R26R	2061	3.9%	3.3%
Chase	AP2-CreER;R26R	13072	2.6%	1.3%
Total Chase	**AP2-CreER;R26R**	**15133**	**3.1%**	**2.2%**

Table 17. Pulse-Chase of AP2-CreER;R26R SV fraction embedded in collagen.

Condition	Genotype	Total Nuclei Counted	% LacZ$^+$ of Total Nuclei	SD
Pulse	Rosa-LacZ (Positive)	263	69.8%	14.4%
Pulse	AP2-CreER (Negative)	3450	0.4%	0.4%
Pulse	AP2-CreER;R26R	7225	1.6%	0.5%
Chase	Rosa-LacZ (Positive)	1101	42.3%	4.2%
Chase	AP2-CreER (Negative)	1308	0.9%	1.2%
Chase	AP2-CreER;R26R	1846	5.8%	2.1%
Chase	AP2-CreER;R26R	1308	10.3%	2.6%
Total Chase	**AP2-CreER;R26R**	**3154**	**7.1%**	**3.1%**

Conclusion and Discussion

Our experiments were designed to address the mechanism of growth and maintenance of the adipose tisssue. To determine whether all the cells in the adipose tissue of adult mouse turn over at the same rate, we utilized the tetracycline-inducible H2BGFP transgenic system. Here, the tetO-H2BGFP transgenic cassette results in labeling of most cells in a given tissue and provides a broad view of the population dynamics. Similar to results with pancreatic β-cells (Brennand et al. 2007), but unlike the results in skin follicular cells, hematopoietic stem cells, muscle satellite cells and intestinal stem cells (Tumber et al. 2004, Brennand et al. 2007), no outlying population of LRCs was identified in the murine adipose tissue. Instead, we found a uniform loss of the H2BGFP labeling with time in adipose tissue, prompting us to suggest homogeneity exists within the adipose pool with respect to replicative potential. Stated otherwise, all the cells within the adipose tissue appear to turnover similarly.

In order to determine cellular turnover and whether cells in the adipose tissue undergo frequent replication, we next assayed the ability of the cells in the adipose tissue to incorporate an artificial nucleotide analog, 5-bromo-2'-deoxyuridine (BrdU), via DNA synthesis. By immunohistochemical analysis of BrdU incorporation we found that within the Perilipin-expressing cells population, 0.6% of the cells had incorporated BrdU per day, and that 1.8% of C/EBPα-positive cells were in S-phase per day. It is important to note that BrdU labeling of Perilipin-expressing adipocytes may result via BrdU incorporation into replicating preadipocytes immediately prior to adipocyte differentiation. We next investigated the expression of Ki67, a well-established marker of cell division, in adipose tissue of C57/BL6 mice at various ages and we found that 4.8% of C/EBPα-positive cells were in the cell cycle at any time. FACS analysis of nuclei from dissociated fat tissue of 8 weeks old wild-type mice showed that the total percentage of Ki67-

positive C/EBPα-positive nuclei in the floating fat sample was 2.36%; of this 0.45% represented C/EBPα-high Ki67-positive events. FACS plots of the stromal/vascular nuclei from dissociated fat tissue of wild-type mice, stained for Ki67 and C/EBPα showed that the total percentage of Ki67-positive C/EBPα-positive nuclei was 3.85%; of this 0.06% represented C/EBPα-high Ki67-positive events, and 3.79% represented C/EBPα-low Ki67-positive events. In addition, performing confocal analysis on whole-mount adipose tissue we counted a total of 4.2% of Ki67 positive nuclei, of this 0.8% represented CD31 Ki67 positive cells, 1.8% of Ki67 positive cells were negative for CD31 and overlapped with Perilipin expressing cells, while for 1.5% of Ki67 positive cells we could not determine the nature of the cellular type.

To directly compare the replicative capacity of cells in the adipose tissue, we performed a lineage tracing analysis to obtain evidence that adipocytes may be capable of giving rise to new adipocytes. We examined white adipose tissue from AP2-CreER;R26R pulse–chased animals and did not observe any loss of lacZ label with time. Therefore, though sufficient turnover of the adipose tissue occurs within two months as determined by our H2BGFP labeling experiments *in vivo*, our lineage-tracing analysis may suggest that one source of new adipocytes may be preexisting adipocytes, as evidenced by the permanent, heritable lacZ labeling within fat cells. According to this hypothesis, the adipocyte population would be maintained at least in part by adipocyte replication. However, 1.9% of the SV fraction positive for LacZ, might represent a population of precursors which proliferate to give rise to a substantial proportion of adipocytes.

Our experiments allowed us to estimate the turnover rate of fat cells in adipose tissue based on the addition of new cells measured by BrdU incorporation and loss of cells measured by the loss of H2B-GFP in the tissue.

There are several possible explanations for the recorded diminution of H2BGFP intensity in adipose tissue:

* **GFP dilution due to high replicative rate of preadipocytes and adipocytes.**

One possibility could be a high replicative rate of cell division, suggesting that all fat cells - mature adipocytes and preadipocytes - contribute equally to fat growth and maintenance in wild-type mice. The finding that mature adipocyte may undergo replication, thereby contributing to the maintenance and expansion of the adipocyte population, would challenge the view that adipocytes are incapable of replication and that the cellular turnover occurring in this adipose tissue results entirely from preadipocyte differentiation.

However, although our data, including our preliminary lineage-tracing experiments, may suggest that mature adipocytes are capable of replication, further experiments are required to formally prove this notion. Specifically, direct evidence of adipocytes replication would be required.

It is very important to remember that the analysis of adipose tissue by immunohistochemistry is quite challenging experimentally. Adipose tissue is highly vascularized and every adipocyte is juxtaposed with multiple capillaries [Crandall et al., 1997], making it very difficult to determine if a nuclear antigen such as Ki67 is a present in the nucleus of an adipocyte or in the nucleus of an adjacent endothelial cell. In addition, macrophage infiltration of fat tissue may occur, adding further complexity by introducing yet another type of cell that is difficult to separate from adipocytes. Moreover, macrophages are known to engulf debris such as dying cells by phagocytosis, leading to an additional potential source of error. Thus our results cannot be considered definitive proof of mature adipocyte replication due to the absence of a nuclear marker for mature adipocyte. High-resolution histological evidence demonstrating fat cells with mitotic figures is critical direct evidence that adipocytes divide. This could be done by digesting adipose tissue to obtain single cells, and thereafter stain adipocytes with established markers of mitosis such as phospho-histone 3 (PH3). Another important experiment that would allow us to determine whether mature adipocytes are capable of replication would be to repeat our lineage-tracing analysis with AP2-Cre mice using mice where Cre recombinase is driven by a gene specifically expressed in mature fat cells, such as Leptin. Unfortunately, to our knowledge, there are no such mice available today.

In addition, a critical experiment would be to use our inducible Cre system to knockout a protein required for replication in mature adipocytes. This would allow us to confirm the validity of our assay but more importantly assess the importance of adipocyte replication for maintenance of adipose tissue mass under normal and obesogenic condition.

Stem cells are defined by the ability to self-renew and differentiate into a variety of cell types. While some adult organs, including the intestine (Cheng and Leblond, 1974), skin (Oshima et al., 2001), blood (Spangrude et al., 1988), and parts of the brain (Doetsch et al., 1999; Reynolds and Weiss, 1992), are maintained by stem cells, others, such as the pancreas (Dor et al., 2004), are not. Pancreatic β-cells are not the only differentiated cell type capable of growth and maintenance without the support of an adult stem cell population. Hepatocytes are highly replicative and not thought to be supported by a facultative stem cell under normal conditions (Alison et al., 2001). Pulse–chase analysis with the tetracycline-inducible H2BGFP label shows that all hepatocytes lose their label at the same rate. Therefore, like the β-cell population (Brennand et al 2007), the hepatocyte population seems to be homogeneous with respect to replicative potential.

We do not know of an example of a mature differentiated cell type that has two populations (one replicative and the other not). We can speculate that when tissues are without an adult stem cell, they are replenished by equal replication of all differentiated cells.

If adipocytes divide, the adipose tissue would represent the first example of a tissue that has both stem cells (or progenitor cells) and mature cells that divide, both thereby contributing to the maintenance of the tissue.

∗ **Dilution of GFP due to apoptosis, necrosis or macrophage engulfment.**

However, until definitive proof that mature adipocytes can undergo cell division is obtained, other interpretations of the diminution of fluorescence intensity have to be considered. One such alternative explanation for our findings could be that

adipocytes are lost due to apoptosis, or macrophage engulfment or necrosis. This supports the idea that adipocytes are postmitotic and that adipose tissue is maintained by stem cell/progenitor cell populations. Numerous data show that adipocyte precursors are capable of both maintaining the progenitor pool and producing adipocytes, and indeed, we found evidence of replication in the SV fraction of adipose tissue in all of our experiments.

An important experiment that would allow us to further elucidate the turnover of adipose tissue would be to measure the percentage of adipose cells undergoing apoptosis. This could be done by fluorescent detection of apoptotic cells by the widely used TUNEL assay or by staining sections of adipose tissue with antibodies specific for Caspase 3, a protein expressed in apoptotic cells.

Two recent publications have provided elegant experimental evidence supporting the long-believed notion that stem/progenitor cells in adipose tissue as a source of newly generated adipocytes. Friedman's and Graff's groups (Rodeheffer et al. 2008, Tang et al. 2008) utilized a range of new *in vivo* tools to elucidate the molecular signature of white adipose stem cells and the niche from which they derive. By using cell surface markers and lineage tracing to identify and isolate stem cells, they demonstrated the capability of these cells to self-renew and, following transplantation, to give rise to functional adipose depots. Furthermore, through *in vivo* experiments they proposed that white adipose progenitors reside within the mural cell compartment of vascular vessels that supply adipose depots. (Zeve et al. 2009, Rodeheffer et al. 2008, Tang et al. 2008). It is believed that the general behavior of stem cells, including phenomena such as quiescence, proliferation, and differentiation, are controlled by the specific environment in which they reside; their niche. Thus the vasculature may provide important cues for adipose stem cells, and antiangiogenic factors, that may be believed to counteract angiogenesis in adipose tissue and inhibit signals from existing vasculature providing trophic support for preadipocytes, might be a possible approach for

treating obesity (Rupnick et al. 2002, Kolonin et al. 2004, Nishimura et al. 2007, Zeve et al. 2009).

The molecular and cellular processes that regulate fat mass remain almost entirely unknown. White adipose tissue is the only tissue in the body that can markedly change its mass after adult size is reached. Indeed, fat mass can range from 2-3% of body weight to as much as 60-70% of body weight in humans. (Hausman, D. B. et al. 2001). This expansion could involve several mechanisms, most widely believed to be due to adipocyte hyperplasia and hypertrophy. The existence of a hyperplastic response suggests the involvement of the stem cell compartment but this statement does not imply that adipose stem cells are the driving force for adipose tissue expansion. It is known that obesity is characterized by an increase in adipocyte size. Our data show that in the Ob/Ob mice model of obesity there is an increase of adipocyte size and adipose tissue replication. Though we cannot assure whether the increased replication is due to mature fat cell division, a progenitor-mediated expansion of the tissue, or macrophages "contaminating" the immunohistochemical analysis, we can speculate that once a stimulus (such as caloric intake greater then expenditure) is prolonged, the hypertrophic response may contribute to metabolic dysregulation which might result in recruitment of new cells from stem cells/precursors.

Given the recent enormous increase in the incidence of obesity, adipocytes and fat is today most often considered a harmful tissue that for therapeutic reasons commonly should be reduced. However, there are clinical instances when increase of fat tissue, through transplantation or stimulation of the endogenous adipogenic machinery, would be expected to be beneficial. In this regard, adipose tissue has been stated useful for various regenerative approaches (Zeve et al. 2009, Hansson et al. 2009). For instance, it has been proposed that the capability of inducing stem cells to form adipose tissue would be beneficial for the treatment of lipodystrophy (Zeve et al. 2009). Another possible application might be in the reconstructive surgery to ameliorate anatomical defect such as wound healing, as several reports

have suggested (Tang et al. 2008, Lu et al. 2008, Rodeheffer et al. 2008). Adipose stem cells have also been proposed in the treatment of women after lumpectomy due to breast cancer (Zeve et al. 2009). In addition to regenerative applications, fat stem cells have been proposed to be used as a cellular source for some diseases such as metabolic dysfunction. Subcutaneous white adipose tissue is thought to play a role in reducing metabolic disorder, so the possibility to isolate, expand and reimplant subcutaneous stem cells has been seen as a useful way to reduce blood glucose, cholesterol levels and cancer risk. In this regard, humans have considerable amount of adipose tissue, it should not be difficult to obtain adipose cells for therapeutic use.

Several studies suggested that brown adipose tissue activity could impact daily energy expenditure (Seale P., Lazar M.A., 2009). Another interesting strategy that has been proposed may be the coaxing white adipose stem cells to adopt a brown fat-like phenotype, in order to enhance energy dissipation after reimplantation (Zeve et al 2009, Seale et al. 2009).

Although obesity is a metabolic disorder ultimately caused by energy imbalance, a greater understanding of adipose tissue growth and maintenance may one day aid in the treatment of obesity. Our data support the notion of a dynamic turnover of adipose tissue, and we also show that in one of the most clinically relevant models of obesity in mice, the rate of adipose tissue replication is significantly increased. It seems reasonable to extrapolate this finding to the human population. We can imagine two timepoints of therapeutic intervention against adipose tissue replication in cases of human obesity. First, it is widely accepted that there is a substantial increase in fat cell number during adolescence and it is believed that an elevated number of adipocytes at the end of this period is a strong predictor of adult obesity (Lloyd et al. 1961, Freedman et al. 2001). The ability to slow the rate of adipose tissue replication during this critical period of adolescent and early adult development may therefore prevent both juvenile and adult obesity. Second, it may be that adult obesity itself is caused, or exacerbated, by elevated rates of precursor

and/or adipocyte replication. If this is true, targeted intervention to reduce adipose tissue replication in adults may facilitate weight loss in obese patients.

Our data should both refocus attention to established questions as well as provide novel and stimulating ideas for the fields of adipocyte biology and obesity. For example, how is turnover of fat issue regulated? Are new adipocytes generated solely from preadipocytes or also from mature adipocytes? When, why, and how do cells in adipose tissue decide to divide? Does replication play a fundamental role in particular conditions such as obesity, regernation following lipectomy, fasting, extreme exercise, or pregnancy? Are the kinetics of adipose tissue turnover different during different stages of life? If so, how is such a phenomenon regulated? When does adipose tissue use stem cell recruitment for the growth and maintenance of the tissue and when is replication used instead? Do adipose stem cells arise *in situ* in the vessel or do they form elsewhere and migrate to the vessel wall? What are the signals that control adipose stem cells biology? Do fat stem cells play an important role in homeostasis and maintenance of the tissue or only in response to particular conditions such as high fat diet? How is the turnover of adipose tissue regulated in terms of the genetic programs for adipogenesis, differentiation, replication and apoptosis?

Answers to these questions has the potential to expand our knowledge of the pathogenesis of obesity, and may open up possibilities for novel therapeutic approaches that may prove to be of great importance in the treatment of obesity and diseases associated with obesity.

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