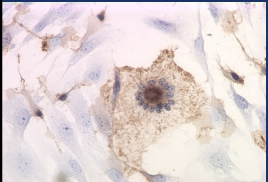


The Immunology of Obesity
20 September 2008
Rome, Italy



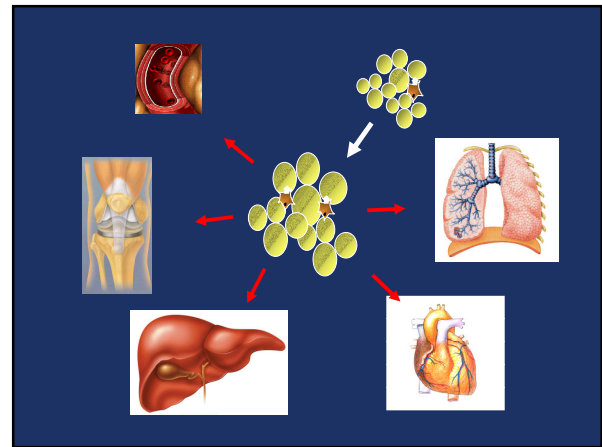

Anthony Ferrante, MD PhD
Naomi Berrie Diabetes Center
Columbia University Medical Center
New York-Presbyterian Hospital

Obesity Induces a Complex Inflammatory State

- Studies dating back to the 1960's document increased circulating concentrations of acute-phase factors in obesity
- In the early 1990's the expression of $TNF\alpha$ by adipose tissue was found to be increased by obesity

Inflammation is Implicated in Obesity-induced Complications


- Atherosclerosis –
 - Endothelial cells, smooth muscle cells
- Insulin resistance
 - Hepatocytes, myocytes, adipocytes
- Reactive airway disease
 - Smooth muscle cells, pneumocytes
- Non-alcoholic fatty liver disease
 - Hepatocytes
- Cancer - Ductal cells, hepatocytes
- Osteoarthritis

?

Inflammation Complications

Mechanisms of Obesity-induced Complications

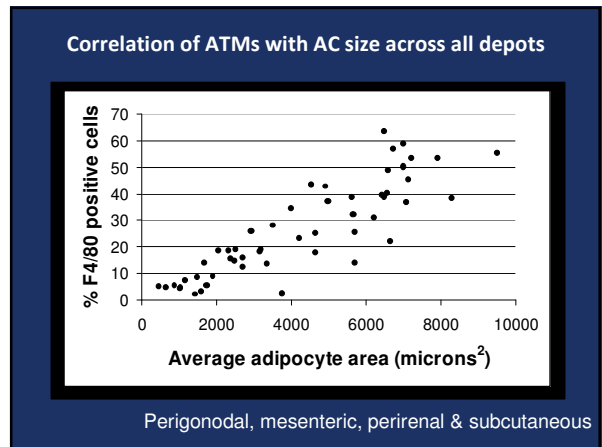
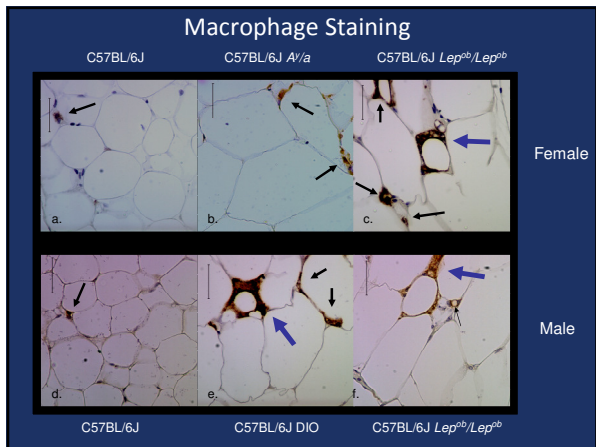
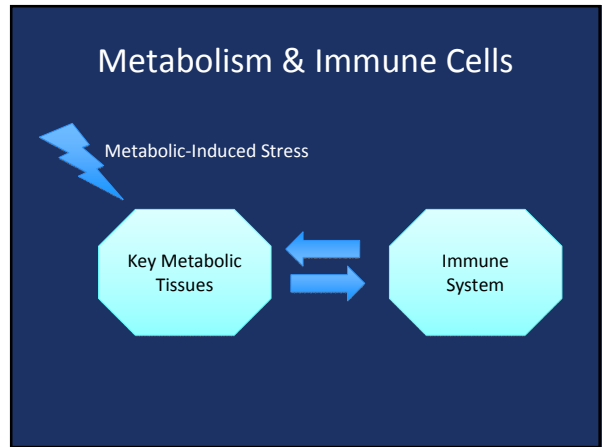
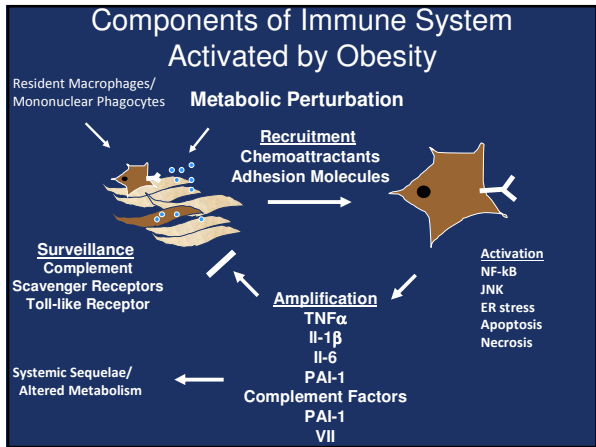
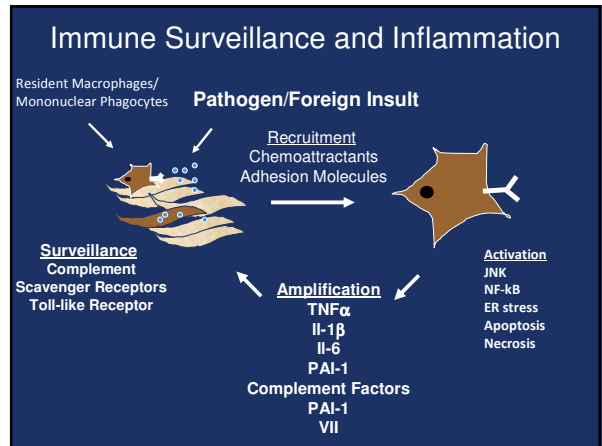


$TNF-\alpha$

Inflammation Complications

Components of Obesity-induced Inflammation

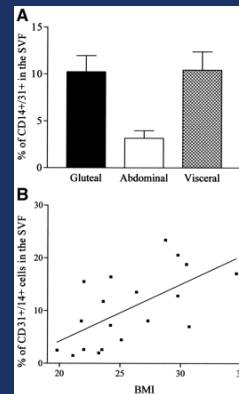
- Inter-cellular inflammatory signals
 - $TNF\alpha$, IL-6, PAI-1, adiponectin, CCL2/MCP-1, complement
- Intra-cellular inflammatory signaling pathways
 - JNK, NF- κ B, UPR/ER-stress



Adipose Tissue Macrophages

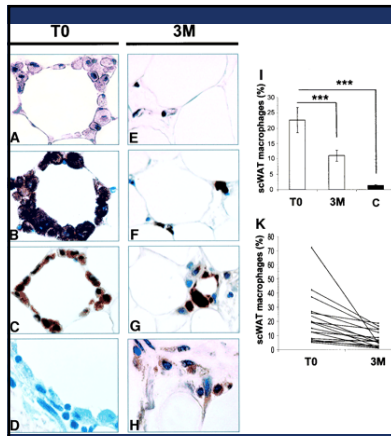
- Obesity induces accumulation of adipose tissue macrophages
- Adipose tissue macrophages express pro-inflammatory genes
- Adipose tissue macrophages are bone marrow derived

Weisberg et al JCI (2003) 112:1796-1808
Xu et al JCI (2003) 112: 1821-1830



Macrophage Content of Adipose Tissue Correlates with Adiposity

Curat et al Diabetes 53:1285-1292, 2004



Reduction in Macrophage Content Following Bariatric Surgery

Cancello Diabetes 54:2277-2286, 2005

Adipose Tissue & Myeloid Phagocytes

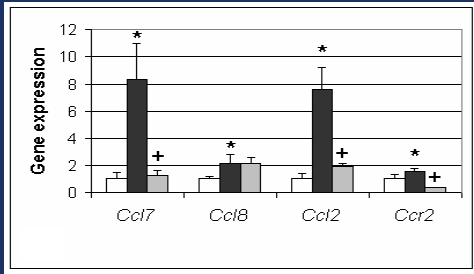
- Macrophages (ATMs) accumulate in proportion to adiposity
- ATM content change in response to changes in body weight
- ATMs in obese subjects are M1 polarized
- Other immune cell populations in adipose tissue are altered by obesity, eg T-cells. These cells are likely to help regulate ATM function

Is Adipose Tissue Unique in the Role of Macrophages/Myeloid Cells in Obesity Induced Inflammation?

CCR2 and Its Ligands

- CCR2 is a high affinity receptor for monocyte chemoattractant proteins (MCPs) including MCP-1 (CCL2), MCP-3 (CCL7) and CCL8
- Each is a member of the chemokine superfamily and belongs in the C-C subfamily.
- MCP-1 has been shown to be critical for classical and non-classical inflammation

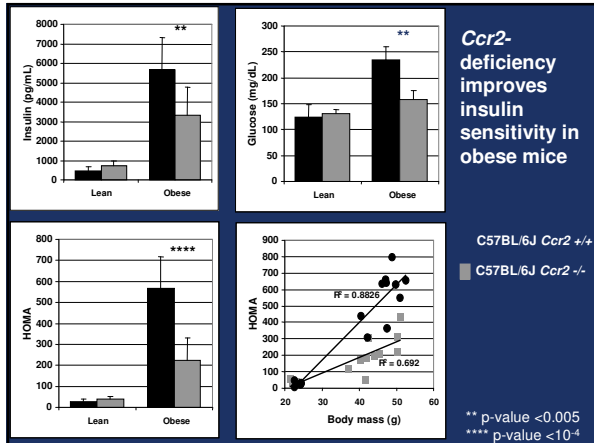
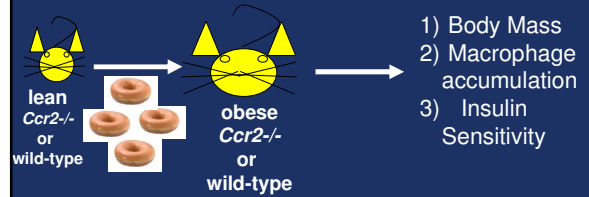
Ccr2 and Ligand Expression in Adipose Tissue



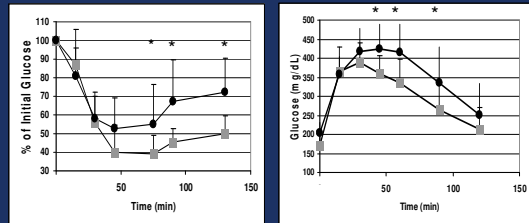
* lean vs obese p-value < 0.05
+obese vs TZD obese p-value < 0.05

□ Lean
■ Obese
■ Obese – pio treated

Hypothesis: CCR2 signaling is required for normal macrophage accumulation in adipose tissue

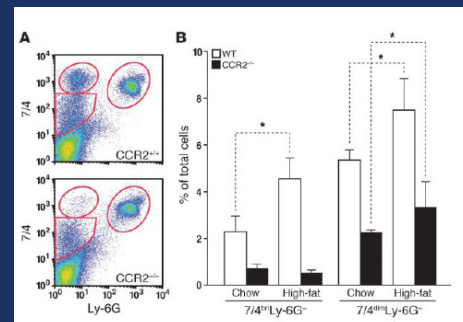


Ccr2-deficiency Improves Glucose Homeostasis in Obese Mice



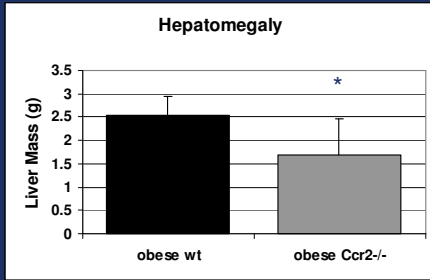
What about other sites of obesity-induced inflammation?

Obesity Induces a Monocytosis



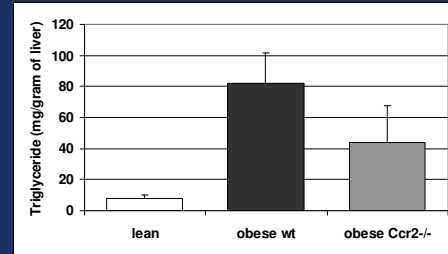
Tou et al. ICI 2007

Reduced Hepatomegaly



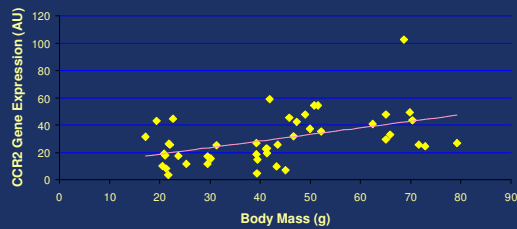
* p-value <0.05

Effects of *Ccr2* Genotype on Hepatic Steatosis



lean wt vs obese wt p-value < 10⁻⁴
obese wt vs obese Ccr2^{-/-} p-value < 0.005

Hepatic Expression of CCR2 & Body Mass



r=0.46; p<0.001

Hepatic Expression of CCL2/MCP-1 and Body Mass



r=0.39; p<0.001

Immune Cells of the Liver

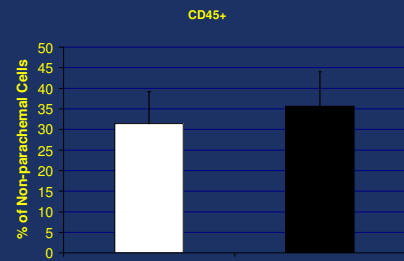


- 1) Perfuse with Collagenase
- 2) Centrifuge to Remove Hepatocytes
- 3) Incubate with anti-bodies
- 4) Sort

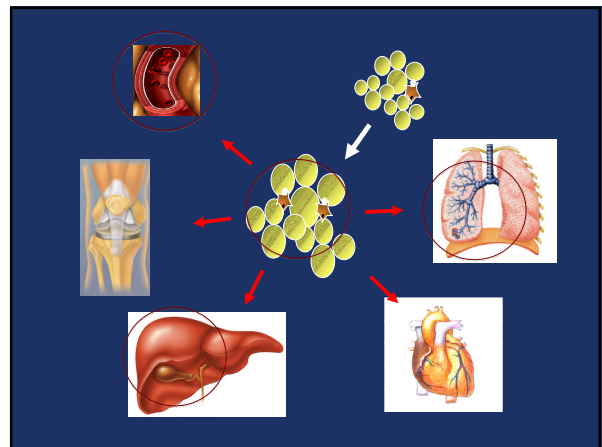
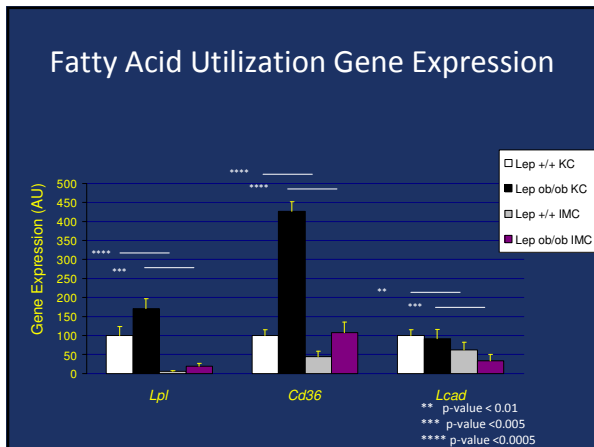
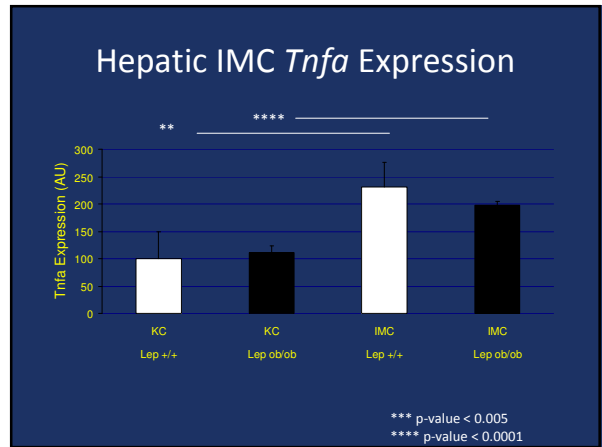
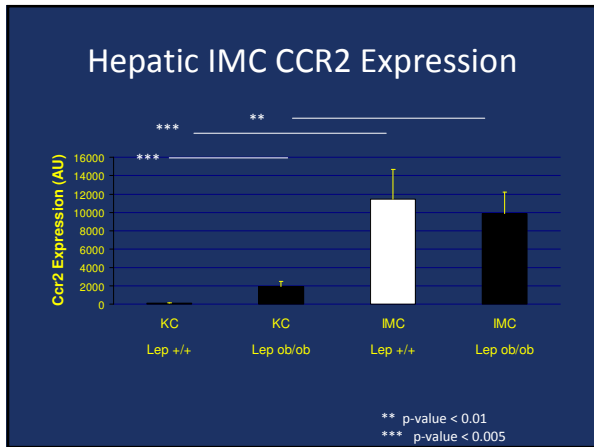
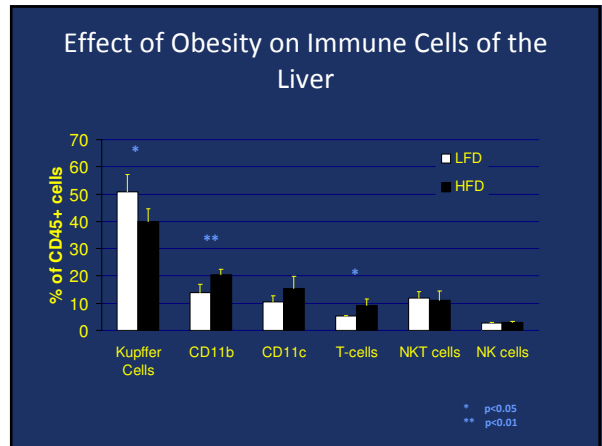
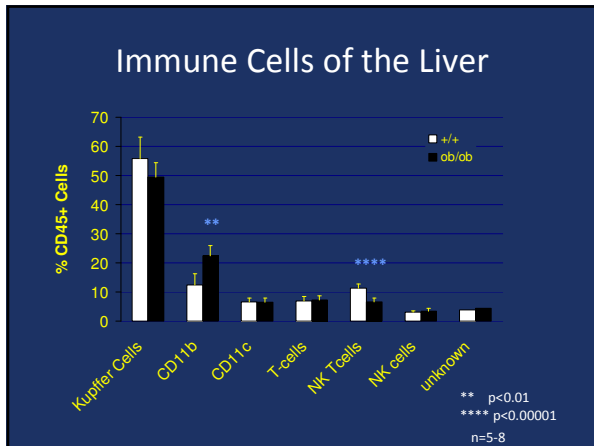
Immune Cells/Leukocytes (CD45) – Heterogenous populations but not well characterized

- Kupffer Cells (F4/80) – Hepatic resident macrophages ~15% of total cells of liver
- T-cells (CD3e) – small but significant populations of cells
- NKT cells (CD3e, NK1.1) – reported to be decreased in obesity
- B-cells (CD19) – very few found in normal livers
- Granulocytes (Ly6G) – very few found in normal livers
- Dendritic cells (CD11c) – reports suggest a role in chemical induce fibrosis
- Other Myeloid cells (CD11b) – not well studied

Effects of Obesity on the Immune Cells Population of the Liver



p-value = 0.09
n=8



Conclusions

- Immune system senses and responds to changes in whole body metabolism by mobilizing and activating mononuclear phagocytes.
- Mononuclear phagocytes contribute to obesity-induced complications, including insulin resistance, hepatic steatosis and atherosclerosis.

Questions?

- Does the systemic activation and mobilization of myeloid cells predispose obese individuals to the development of inflammatory diseases, including AO?

Does Obesity Contribute to OA by a Mechanical-Independent Mechanism

Table 1. Relationship between hand OA and body weight from birth to age 53 years*

Age, years	Men			Women		
	OA	No OA	P	OA	No OA	P
Birth	3.38	3.48	0.004	3.33	3.32	0.65
2	13.1	13.3	0.12	12.6	12.6	0.79
4	17.3	17.5	0.20	17.1	17.0	0.23
7	23.1	23.0	0.84	22.6	22.6	0.75
11	34.5	34.2	0.45	35.4	34.8	0.13
15	52.4	51.6	0.28	51.9	51.9	0.89
26	74.6	73.1	0.03	59.3	59.1	0.68
36	77.5	76.0	0.07	62.4	62.0	0.58
43	79.3	77.6	0.04	66.1	65.7	0.63
53	85.4	83.3	0.02	71.4	71.7	0.76

* Values are the average weight (in kg). OA = osteoarthritis.

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