Cell Metabolism
Review

Mechanisms and Metabolic Implications of Regional Differences among Fat Depots

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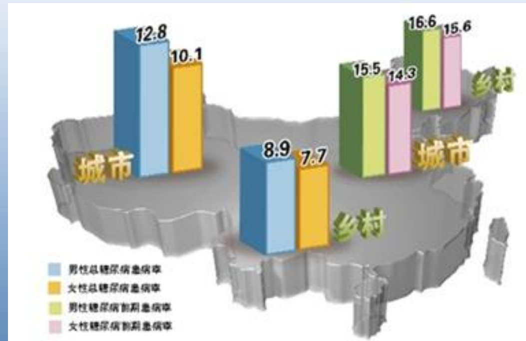
Introduction

T2D: 90%

The widespread of diabetes

现实严峻

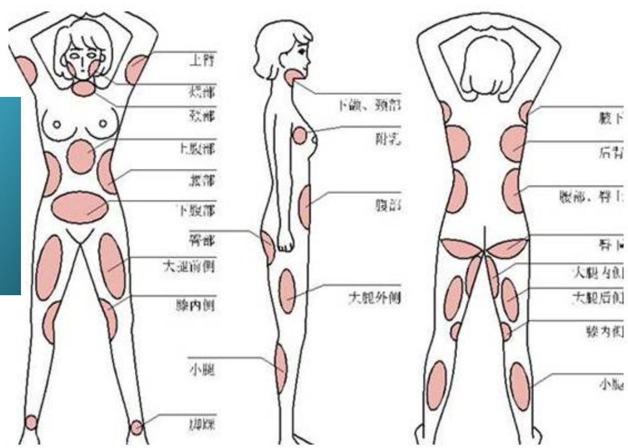


中国糖尿病
患者持续增加

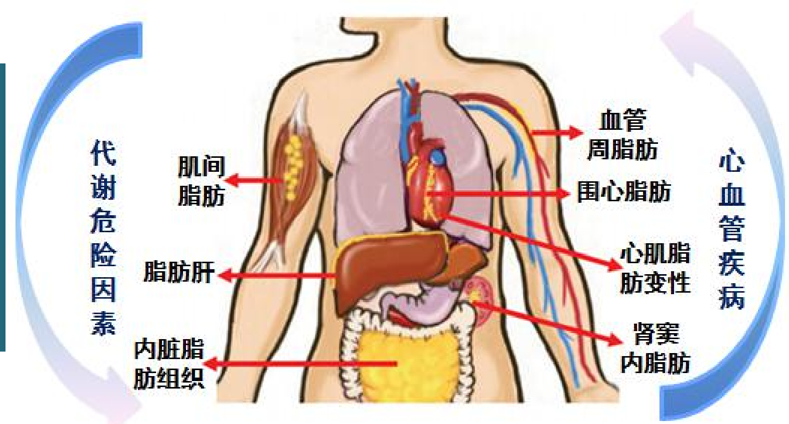
男性糖尿病比
女性风险高20%

肥胖和糖尿病主要
是机体脂代谢紊乱造成

正常人体脂肪分布

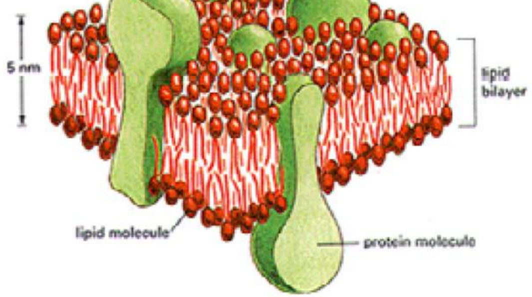


异位脂肪储存及潜在的全身及局部效应

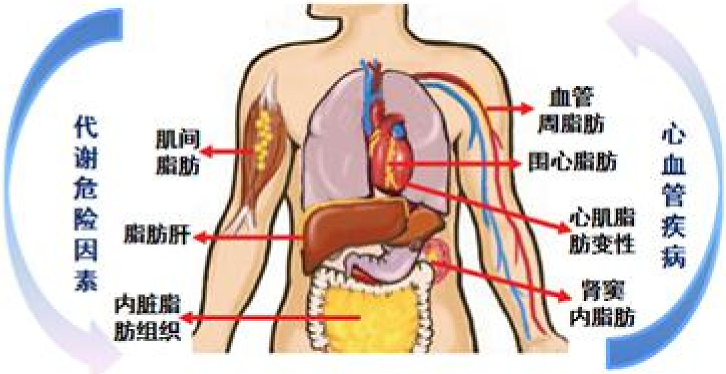


Fat-Tissue Function

Major Components of Membranes



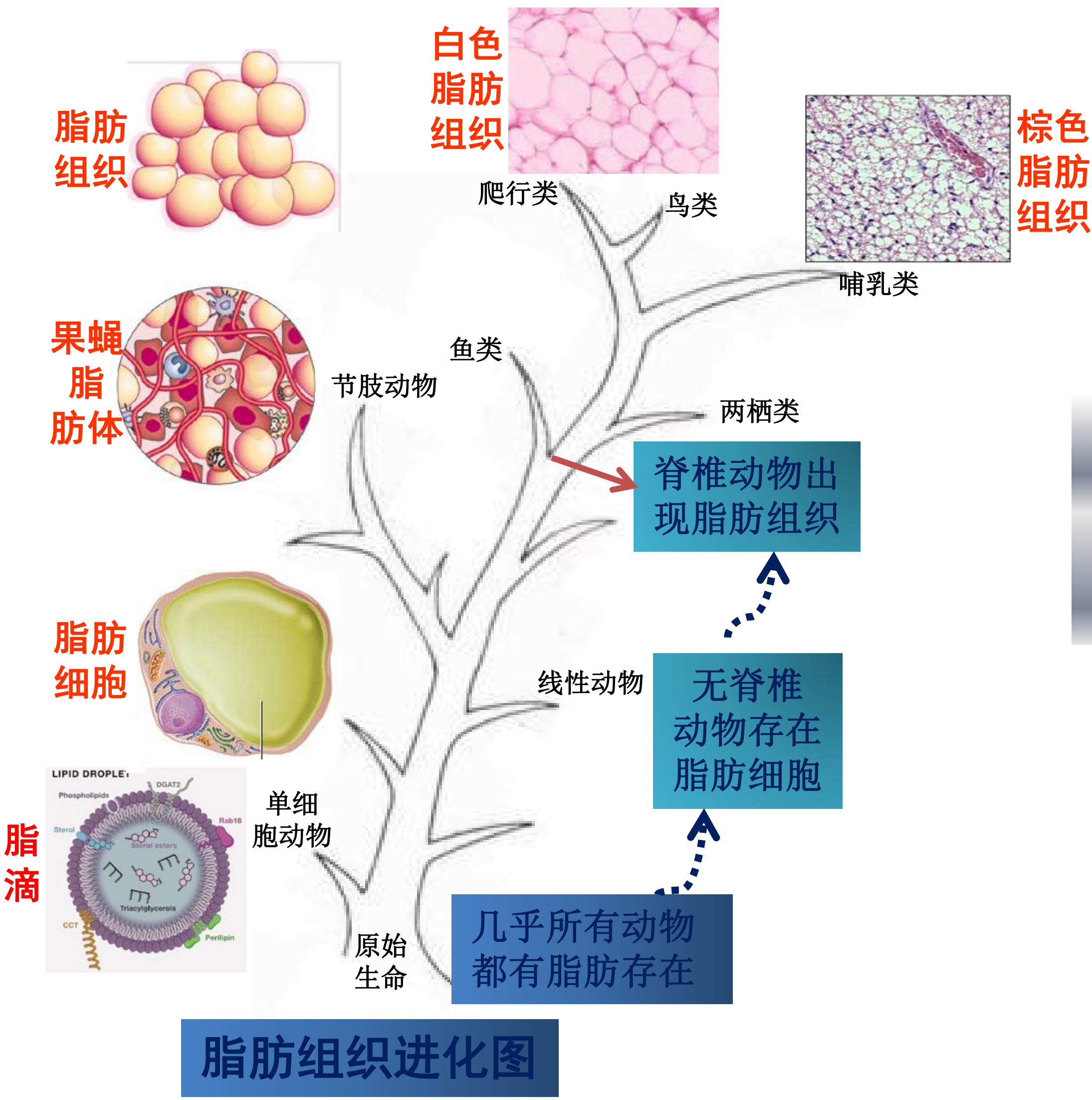
防水

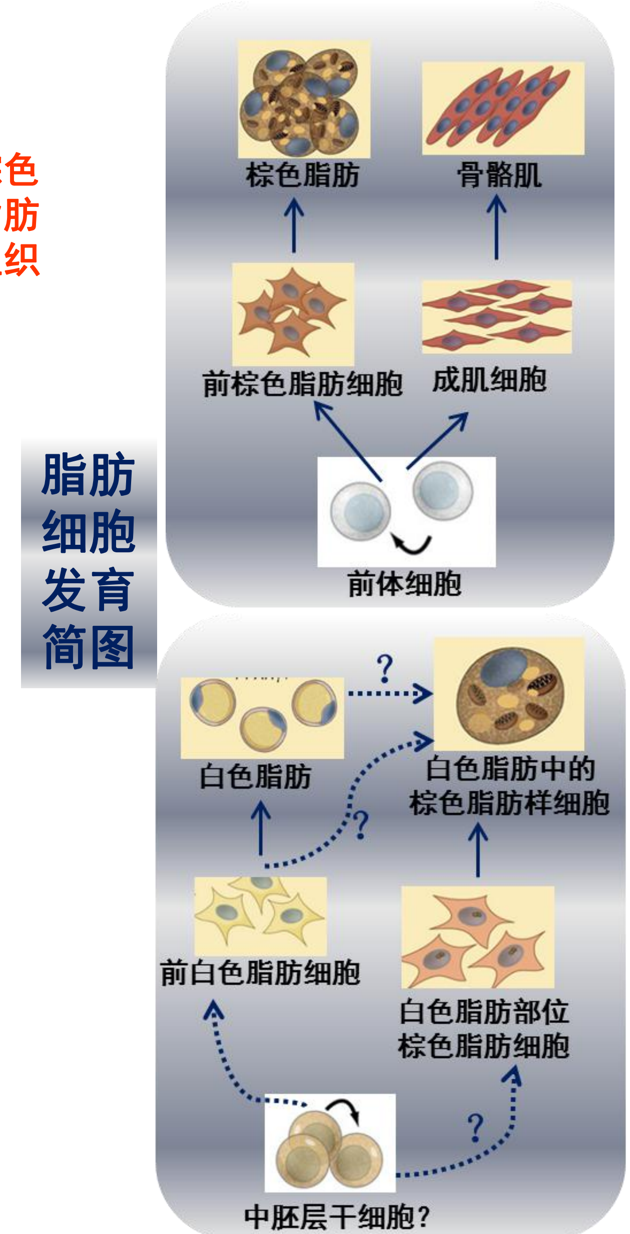


脂肪储存和疾病

脂类功能

脂肪组织的演化


脂肪
组织
白色
脂肪
组织
棕色
脂肪
组织
爬行类
鸟类
哺乳类
果蝇
脂
肪体
鱼类
节肢动物
两栖类
脊椎动物出
现脂肪组织
脂肪
细胞
线性动物
无脊椎
动物存在
脂肪细胞
LIPID DROPLET
脂
滴
单细
胞动物
原始
生命
几乎所有动物
都有脂肪存在
脂肪组织进化图


脂肪
细胞
发育
简图
棕色脂肪
骨骼肌
前棕色脂肪细胞
成肌细胞
前体细胞
白色脂肪
?
白色脂肪中的
棕色脂肪样细胞
?
前白色脂肪细胞
白色脂肪部位
棕色脂肪细胞
?
中胚层干细胞？

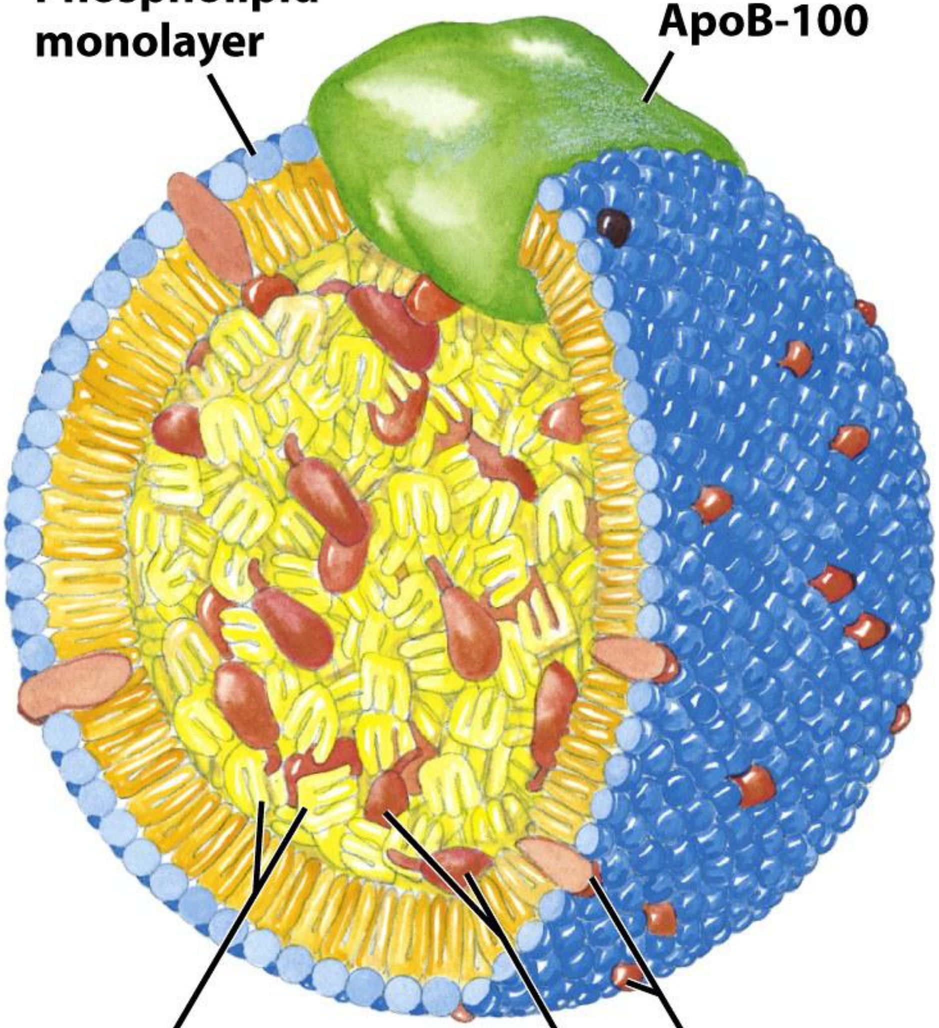
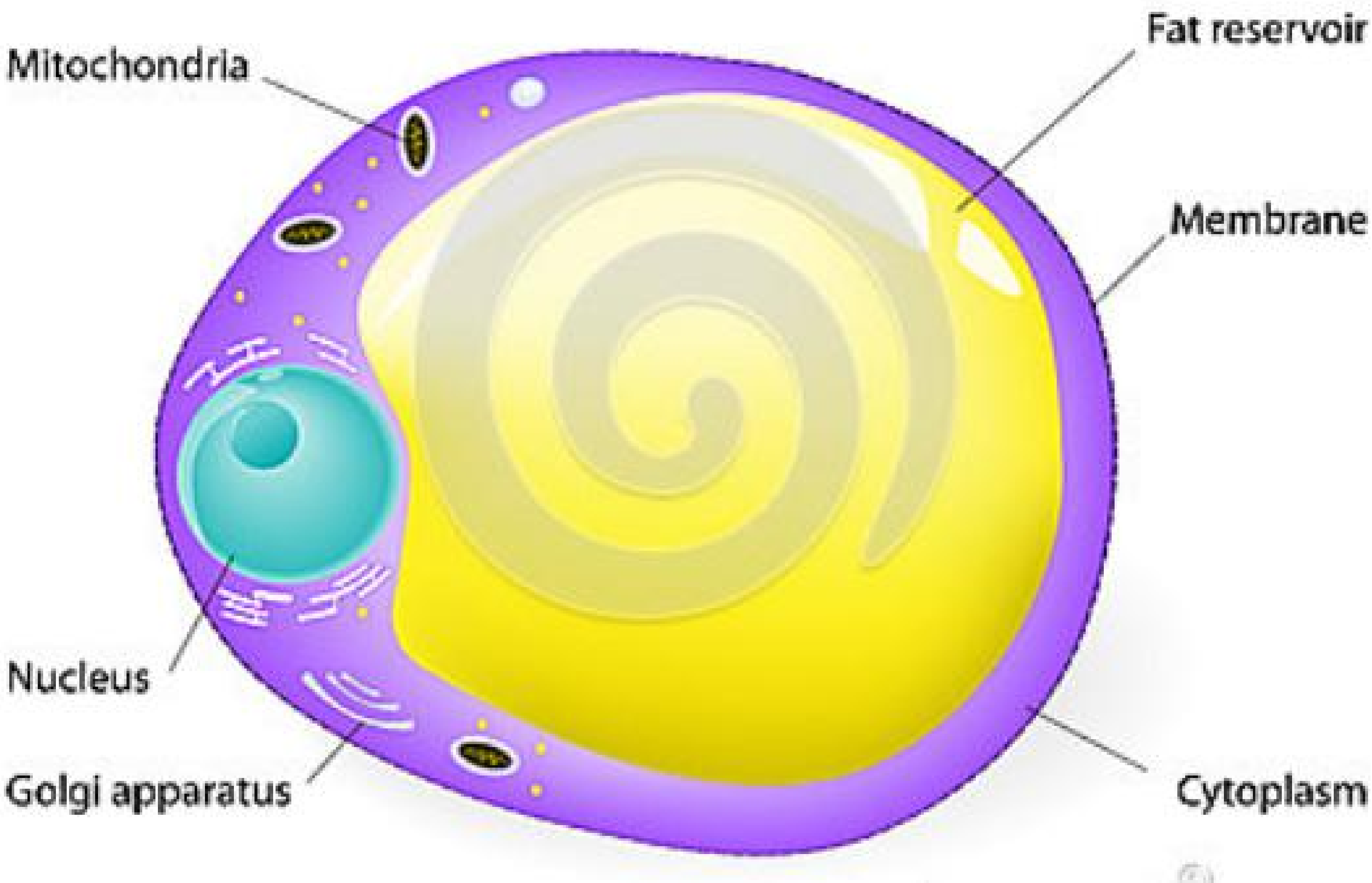


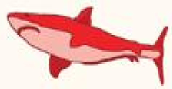
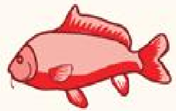
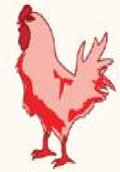
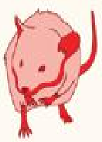
Figure 21-39a
Lehninger Principles of Biochemistry, Fifth Edition

ADIPOCYTE


Mitochondria
Fat reservoir
Membrane
Nucleus
Golgi apparatus
Cytoplasm

脂肪组织分布的多样性

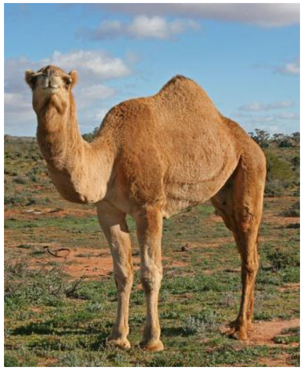
不同动物脂肪储存部位不一样　　*Gesta et al. Cell. 2007*

Species	 *Caenorhabditis elegans*	 *Drosophila melanogaster*	 *Carcharodon carcharias*	 *Cyprinus carpio*	 *Xenopus laevis*	 *Gallus gallus domesticus*	 *Mus musculus*	 *Homo sapiens*
Fat storage	Stored in intestinal cells	Stored in the "fat body"	Stored in liver	Stored in WAT	Intra-abdominal WAT (no sub-cutaneous WAT)	Subcutaneous and internal WAT	Subcutaneous and internal WAT	Subcutaneous and internal WAT

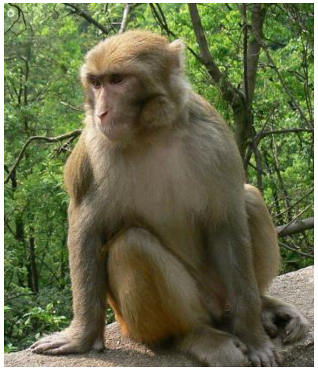
哺乳动物脂肪储存部位差异很大

皮下

驼峰



全身



全身/浅皮下脂肪

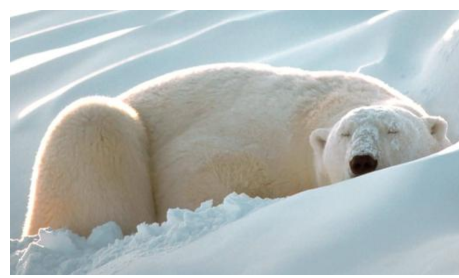
脂肪组织分布的多样性

相近、同种动物脂肪储存的主要部位不一样

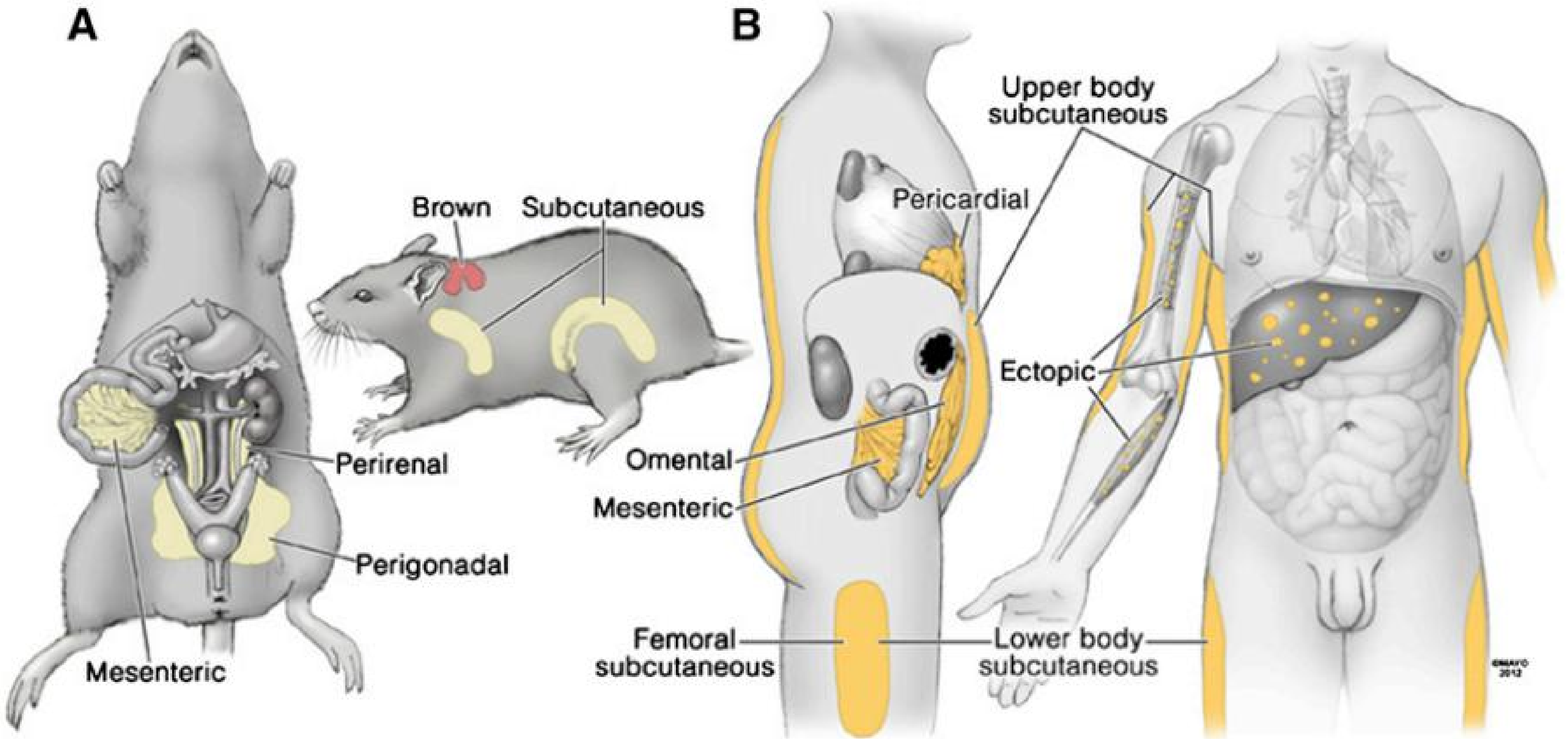



节俭基因：人体在进食期积极存储能量以备饥饿期消耗的基因

“节俭基因型”假说



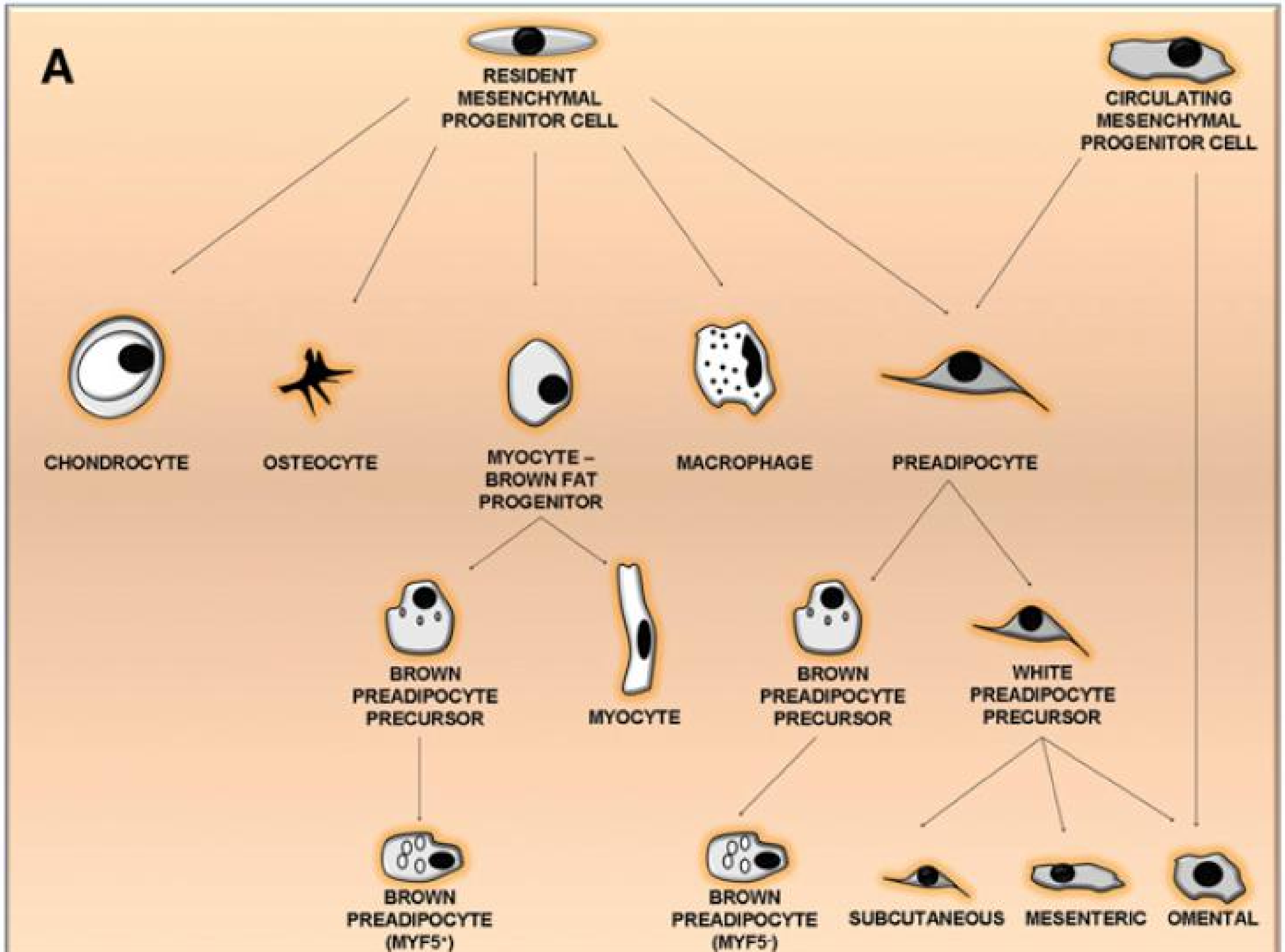

冬眠的动物和迁徙的鸟类异位脂肪存储不会导致相应的疾病



Anatomy of Major Fat Depots in Rodents and Humans

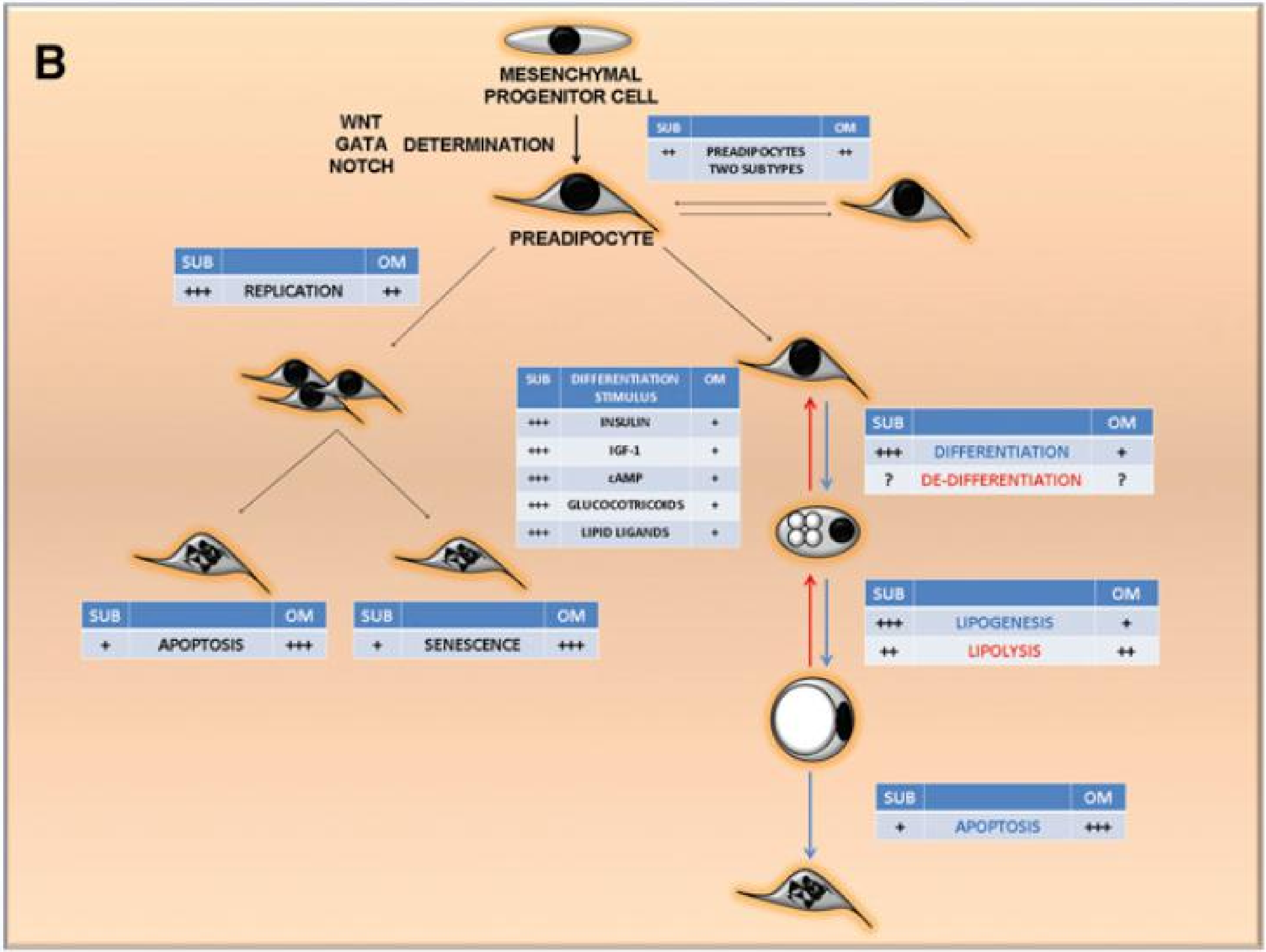
intra-abdominal:omental and mesenteric depots,also termed visceral fat
lower-body:gluteal fat,subcutaneous leg fat,and intramuscular fat
upper-body: subcutaneous fat

Cellular Mechanisms of Fat Growth and Function

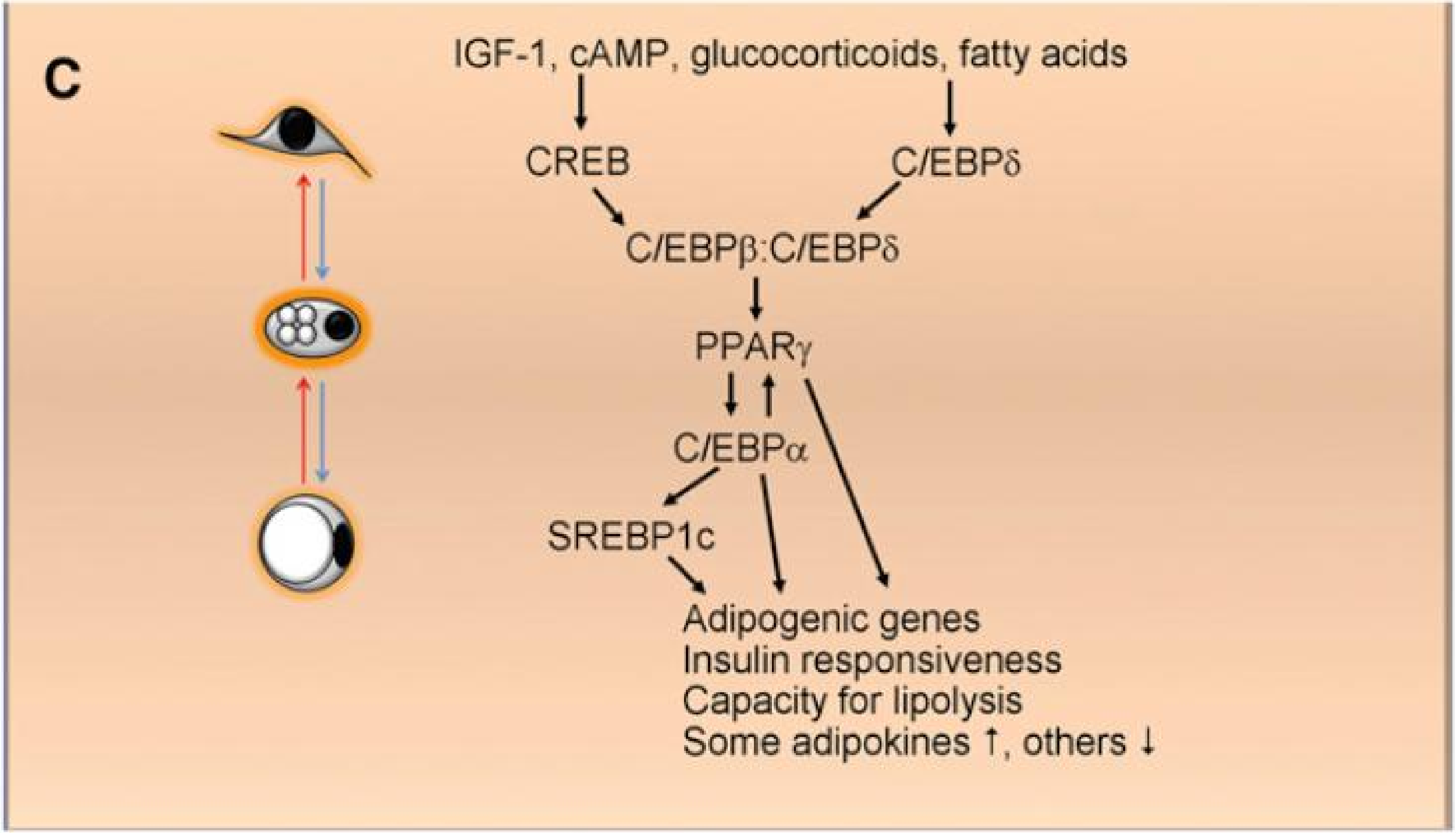


Circulating progenitors may contribute, especially to visceral fat developent

Regional variation in fat-tissue cell dynamics



preadipocytes can replicate, differentiate into adipocytes, or possibly revert into multipotent progenitors again



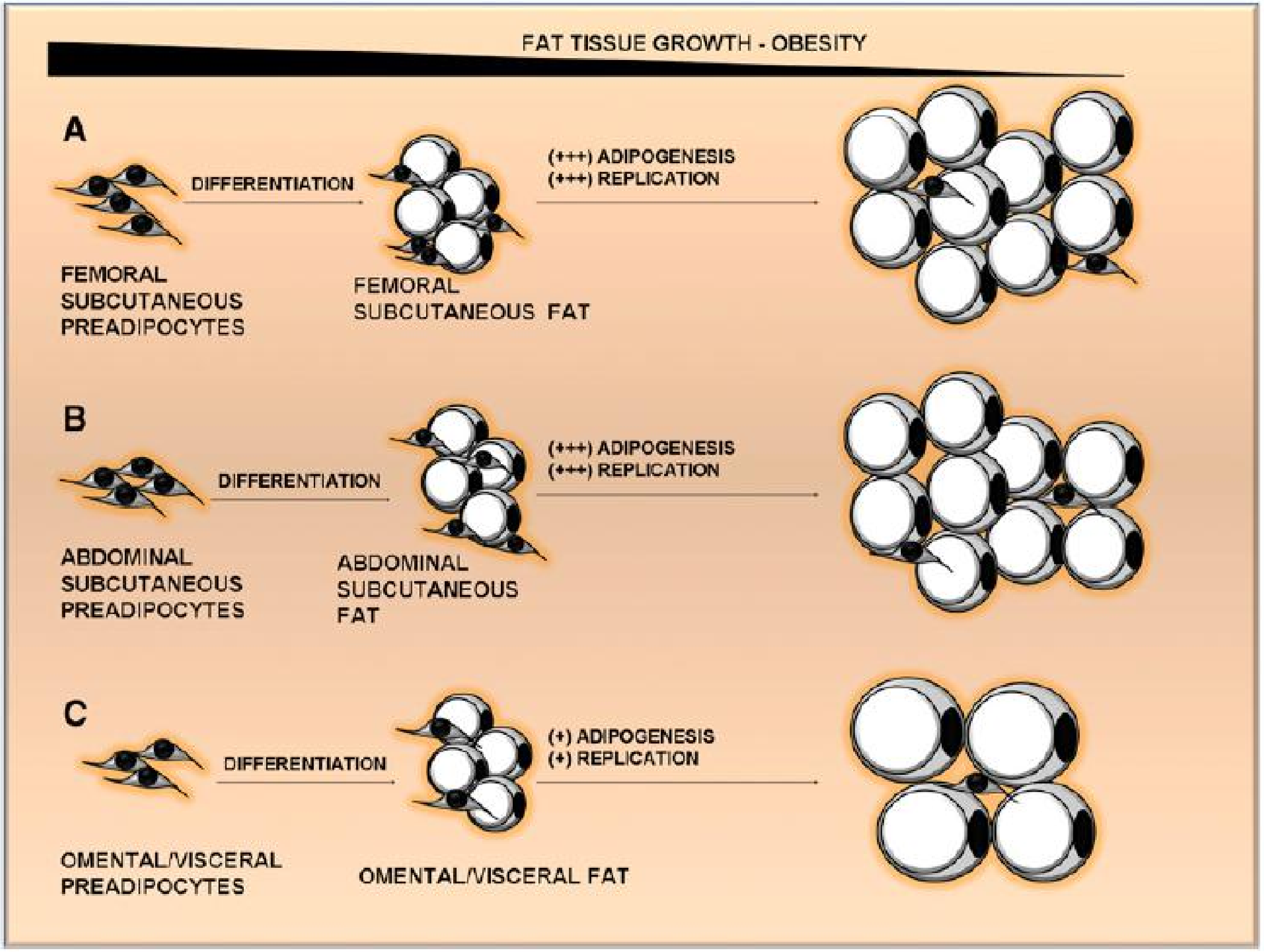
Key transcription factors involved in adipogenesis.

Table 1. Adipokines Reported to Exhibit Fat-Depot-Specific Expression

Adipokine or Secreted Factor	Source Cells	Depot	References
Leptin*	fat cells	subcutaneous > omental	(Wiest et al., 2010)
Adiponectin* HMW	fat cells	omental > subcutaneous	(Kovacova et al., 2012)
PAI-1	preadipocytes	possibly, omental > subcutaneous	(Xu et al., 2012)
IL-6*	preadipocytes, macrophages, activated endothelial cells, large fat cells	visceral > subcutaneous	(Fontana et al., 2007)
TNF-α*	preadipocytes, macrophages, adipocytes	mesenteric > omental = subcutaneous	(Cartier et al., 2008; Xu et al., 2012)
MCP-1*	preadipocytes, macrophages	visceral > subcutaneous	(Madani et al., 2009; Miller et al., 2011)
Angiotensinogen	fat tissue	omental > subcutaneous	(Dusserre et al., 2000; van Harmelen et al., 2000)
RANTES*	stromal vascular fraction, fat cells	gastric fat pad > omental = subcutaneous	(Madani et al., 2009)
CSF-1	endothelial cells, fibroblasts	visceral > subcutaneous	(Harman-Boehm et al., 2007)
Omentin	stromal vascular cells	omental > subcutaneous	(Yang et al., 2006)
RBP4	preadipocytes, adipocytes	visceral < subcutaneous	(Kos et al., 2011)
Chimerin	unknown	visceral < subcutaneous	(Alfadda et al., 2012)
Vaspin	fat cells	visceral > subcutaneous	(Hida et al., 2005; Klöting et al., 2006)

Preadipocytes generate adipokines, paracrine factors, hormones, and metabolic signals in a manner distinct from fat cells. Several adipokines are secreted in a fat-depot-dependent fashion

Regional Differences in Preadipocyte Characteristics Replication



Mechanisms of Fat-Tissue Growth during the Progression of Obesity Vary among Depots

Differences in cell-dynamic properties of preadipocytes are partly cell autonomous

RAT	perirenal preadipocytes	>	epididymal preadipocytes		
HUMAN	abdominal subcutaneous preadipocytes	>	mesenteric preadipocytes	>	omental preadipocytes

replication

Adipogenesis

- abdominal subcutaneous preadipocytes had a greater capacity for adipogenesis than omental cells
- PPARγ and C/EBPa expression is higher in human abdominal subcutaneous than in omental differentiating preadipocytes

adipogenesis appears to vary among depots

Apoptosis and Senescence

- Apoptotic fat cells are more abundant in human omental than abdominal subcutaneous fat, which may induced by serum deprivation or TNF-α
- Cellular senescence may contribute to regional variation in age- and obesity-related increases in fat-tissue inflammation, glucose intolerance, loss of capacity to store fat in subcutaneous depots, and lipotoxicity.

Inherent Differences

- Genome-wide expression profiles of primary preadipocytes cultured in parallel from different depots of mice and humans are highly distinct. Expression of >500 genes varies significantly among human abdominal subcutaneous, omental, and mesenteric preadipocytes and fat tissue.
- Whether developmental regulators directly cause regional differences in preadipocyte and fat-depot characteristics is being actively in vestigated.
- Most developmental genes are subject to epigenetic regulation

A Special Role for Leg Fat?

- **leg fat appears to serve an important role in disposing of excess dietary fat in women**
- **Adipose tissue lipolysis in leg fat is normally exquisitely sensitive to insulin this makes lower-body depots an ideal place to store fat when it is ingested in excess of short-term energy needs.**
- **Greater amounts of leg fat signal a lesser metabolic risk and a more normal fatty-acid profile, although whether leg fat plays a protective role or (opposite of visceral fat) signals generally normal function of subcutaneous fat remains to be determined.**

Mesenteric Fat: An Underappreciated Role?

- **Mesenteric fat may make an important contribution to metabolic dysfunction, acting in a manner distinct from omental fat.**
- **The cellular and gene-expression properties of human mesenteric fat are cell autonomously distinct from omental fat.**

Metabolically Protective Role of Subcutaneous Fat

- **Certain subcutaneous fat regions appear to be metabolically, immunologically, and mechanically protective.**
- **The high capacity for certain subcutaneous regions to generate new fat cells may prevent visceral fat enlargement and systemic lipotoxicity.**

Intra-abdominal Fat: Cause or Indicator?

- **Central fat is associated with elevated risk for diabetes, hypertension, atherosclerosis, dyslipidemia, and cancers.**
- **In normal-weight or moderately overweight people, visceral obesity is strongly associated with insulin resistance, but in severe obesity, it is a weak independent predictor.**

Conclusions

- Fat distribution is closely linked to metabolic disease risk.
- Distribution varies with sex, genetic background, disease state, certain drugs and hormones, development, and aging.
- Preadipocyte replication and differentiation, developmental gene expression, susceptibility to apoptosis and cellular senescence, and adipokine secretion vary among depots.
- How interdepot differences in these molecular, cellular, and pathophysiological properties are related is incompletely understood.
- Whether fat redistribution causes metabolic disease or whether it is a marker of underlying processes that are primarily responsible is an open question.

thanks