

De Novo Adipogenesis; Significance to Nutrition, Obesity, and Metabolic Homeostasis

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Traditionally, adipose tissue was primarily considered as a nutrient storage place and a cushion to protect vital organs from mechanical damage. This view has changed considerably since the past decade due to the discovery of several adipose tissue derived hormones (adipokines) such as leptin, FGF21 and adiponectin with important physiological regulatory functions [1] and the dysregulation of adipose tissue functions during diseases including metabolic syndrome, type 2 diabetes etc. In this respect, adipose tissue biology has come under renewed scrutiny and several new research areas are being explored. One such topic is adipogenesis or *de novo* formation of adipocytes from the mesenchymal progenitor cells, as known as neoadipogenesis. This process is of importance because it has been shown that under chronic over-nutrition state, neoadipogenesis can prevent metabolic dysfunction and can help to maintain systemic metabolic homeostasis.

White adipocytes are located in various fat “depots” including subcutaneous, visceral and omental depots. Systemic signals, especially insulin secreted from pancreatic islet cells upon feeding, causes these depot resident adipocytes to absorb circulating nutrients and store them as lipid droplet. In times of nutrient deprivation, hormones such as glucagon or noradrenaline stimulate adipocytes to release nutrients in the form of non-esterified fatty acids and glycerol from the lipid droplet to be used by other organs in the body. However, in times of chronic nutrient excess, resembling modern western diet, adipocytes initially increase in size to accommodate excess nutrient (also known as adipose hypertrophy). During this time, adipocyte size can increase considerably but there is an upper limit these adipocytes can reach; bigger adipocytes are not metabolically healthy and do not secrete adipokines properly [2] and eventually fails to respond to anabolic hormones to absorb nutrient, contributing into systemic nutritional overload [3]. In addition, metabolically dysfunctional adipocytes as well as immune cells attracted to such depots including T cells and macrophages secrete pro-inflammatory cytokines such as Tumor Necrosis Factor (TNF), Interferon (IFN), IL6 and angiotensin II [4-7]. Such adipose hypertrophy has been linked with insulin resistance and type 2 diabetes development [8].

Mesenchymal stromal cells (MSC) are tissue resident multipotent progenitors that differentiate into specific cell types in response to various stimulatory conditions [9]. These cells are characterized by their fibroblast like appearance, ability to adhere to plastic culture plate, and the expression of specific cell surface markers [10]. Adipose tissue resident MSCs differentiate into mature adipocytes to store excess nutrients under conditions of prolonged metabolic stimulation. During this process, MSCs first commit to the adipocyte lineage by inducing Bone Morphogenic Protein (BMP) pathway [11,12], thereby forming preadipocytes that are morphologically indistinguishable from MSCs. These preadipocytes then undergo adipogenic differentiation, during which preadipocytes accumulate lipids and form functional, insulin- sensitive mature adipocytes. This *de novo* adipogenesis, also known as adipose hyperplasia, rather than adipose hypertrophy, plays positive roles in controlling nutrient homeostasis by promoting nutrient absorption and preventing ectopic lipid deposition. Several factors impact neoadipogenesis [13], specially pro-inflammatory cytokines IFN, TNF and IL6 are known to inhibit this process. Interferon- γ (IFN- γ) is a key mediator of the metabolic inflammation circuit and heavily contributes to metabolic dysfunction. Although

the effects of IFN- γ exposure in pre-adipocyte and mature adipocyte has been investigated thoroughly, its effect on adipose MSC remains largely unknown. Active research in this field are ongoing to elucidate the molecular mechanisms of action of these pro-inflammatory cytokines on adipogenesis.

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