

Thrombospondin1 Plays an Important Role in Obesity Associated Inflammation and Insulin Resistance

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Obesity is prevalent worldwide and is associated with the development of insulin resistance and type 2 diabetes. Obesity-induced chronic low-grade inflammation has been suggested to be an important mechanism for the development of IR [1]. Adipose tissue is a key organ for this chronic inflammatory response. Increased accumulation of adipose tissue macrophages (ATMs) has been demonstrated in obese rodents and humans by numerous studies [2,3]. It is now well established that ATMs are the primary source of inflammatory cytokine production in adipose tissue and play a key role in obesity-induced chronic low-grade inflammation and IR [2]. Although there have been some advances in the study of ATMs in obese conditions [2,4,5], the mechanisms underlying ATMs recruitment and activation remain to be determined.

Thrombospondin1 (TSP1) is a major component of platelet alpha granules [6,7]. TSP1 acts as an immediate early response gene, exhibiting rapid but transient induction by growth factors and stress in many cell types including adipocytes and macrophages [8-12]. TSP1 exists as both a component of the extracellular matrix and as a soluble molecule found in various body fluids and in the cell culture conditioned medium. TSP1 is a 420-450 kDa homotrimer with individual subunits of approximately 145 kDa. The diverse biological activities of TSP1 have been mapped to specific domains of the molecule by interaction with different cell surface receptors [13]. TSP1 is a multifunctional matricellular protein and plays an important role in cardiovascular and renal diseases [14-18]. TSP1 also plays a role in inflammation and obesity. TSP1 is up-regulated in developing adipose tissue of mice with diet or genetically induced obesity [19]. The expression levels of TSP1 are greater in the visceral adipose tissue than in the subcutaneous adipose tissue of obese humans [12]. In obese, insulin resistant humans, adipose tissue TSP1 expression was up-regulated and associated with adipose inflammation and IR [20], suggesting that TSP1 may play a role in obesity-induced IR. This is supported by our recent studies [21]. By using TSP1 deficient mice, our recent studies revealed a novel role for TSP1 in regulating macrophage recruitment and activation in adipose tissue that contributes to inflammation and IR in a high fat Diet Induced Obese (DIO) mouse model [21]. After 16 weeks of high fat diet (HF, 60% fat) feeding, TSP1 levels in adipose tissue (both adipocytes and stromal vascular cell fraction) were significantly increased in Wild Type (WT) mice. TSP1 deficiency did not affect the development of HF-induced obesity; throughout the study, body weight and fat mass increased similarly between the TSP1 deficient mice and WT mice. However, obese TSP1 deficient mice had improved glucose tolerance and systemic insulin sensitivity compared to the obese WT mice, which was accompanied by decreased ATMs accumulation and decreased adipose and systemic inflammation. Furthermore, *in vitro* studies demonstrated that TSP1 is an important regulator of macrophage function. It acts as a chemoattractant for macrophages and also promotes inflammatory phenotype of macrophages. Further determination of the mechanisms by which TSP1 regulates macrophage function will lead to development of novel therapeutic targets for treatment of obesity related diseases.

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Received December 07, 2012; Accepted December 07, 2012; Published December 10, 2012

Citation: Wang S (2012) Thrombospondin1 Plays an Important Role in Obesity Associated Inflammation and Insulin Resistance. *J Obes Wt Loss Ther* 2:e109. doi:[10.4172/2165-7904.1000e109](https://doi.org/10.4172/2165-7904.1000e109)

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