Biomedical Research and Therapy 2014, 1(4): 121-125
ISSN 2198-4093
www.bmrat.org

DOI 10.7603/s40730-014-0019-0

REVIEW

The Engimatic WNT signaling and Mesenchymal stem cell Adipogenesis: Implications for Metabolic Disorders

Nidhi Anil[1,*]

[1] Centre for Stem Cell & Tissue Engineering, Panjab University, Chandigarh – 160014, India.
*Corresponding author: drnidhianil@gmail.com

Received: 07 September 2014 / **Accepted**: 17 September 2014 / **Published online**: 19 September 2014

Abstract— The past decade has witnessed a sudden surge in the obesity prevalence worldwide. Obesity has been linked to several chronic metabolic disorders including diabetes, hyperlipidemia and atherosclerosis. Due to this there is an immense interest in understanding the intricate aspects of adipogenesis, specifically pertaining to the study of the mechanisms through which various signaling pathways regulate adipocyte differentiation. One such enigmatic signaling pathway regulating adipogenesis is the WNT signaling Pathway. The present review focusses on the role of WNT signaling on Adipogenesis and its relationship with the development of metabolic disorders.

Keywords— Adipogenesis, Mesenchymal stem cell, Metabolic disorders, Wnt signaling.

INTRODUCTION

Obesity is a global health burden, with an estimated prevalence of 3.5 billion adults worldwide (Gortmaker et al., 2011; Misra and Shrivastava, 2013). The obesity epidemic has been linked to the development of several metabolic complications including metabolic syndrome which is a triad of type II diabetes, hypertension and atherosclerosis (Kahn and Flier, 2000). Adipogenesis is a central phenomenon which serves as a key regulator of homeostasis and metabolism. During adipogenesis mesenchymal stem cells precursors differentiate into mature adipocytes (Farmer, 2006). Several transcription factors including peroxisome proliferator activated receptor gamma PPAR γ, CCAAT/enhancer binding proteins C/EBPα & β are known to coordinately control the adipogenic program (Rosen et al., 2000; Wu et al., 1999). Recent reports have highlighted the role of extracellular or circulating regulator factors in the regulation of adipogenesis (Christodoulides et al., 2009), one such extracellular signaling pathway known to regulate adipogenesis is the WNT signaling pathway. Wingless type MMTV integration site (WNT) signaling pathway consists of several secreted glycoproteins known to regulate several cellular processes (Prestwich and Macdougald, 2007). In the current scenario of an obesity epidemic and its interplay with the development of metabolic disorders, there is an urgent need to understand the underlying mechanisms involved in the development of adipocytes i.e from the commitment phase to the differentiation phase, since dysregulated adipogenesis is often known to prelude to the development of metabolic syndrome. The present review focuses on understanding the role of WNT signaling pathway in regulating the mesenchymal stem cell fate, obesity and type II diabetes.

MESENCHYMAL STEM CELL: GENERAL CHARACTERISTICS AND ADIPOCYTE LINEAGE COMMITMENT

Mesenchymal stem cells (MSC) are multipotent, adherent, fibroblastoid stromal cells capable of differen-

tiating into multiple cell types including adipocytes, oestocytes and chrondocytes (Caplan, 1986; Piersma et al., 1985). Mesenchymal stem cells where first identified in the bone marrow, however other sources of MSC's include adipose tissue and skeletal muscle. Bone marrow BMSC expressing various cell surface markers including CD44, CD29, CD73, CD105 and are negative for all hematopoetic markers (Chamberlain et al., 2007). The adipogenesis from mesenchymal stem cell precursors involves two distinct phases, the determination phase which involves the commitment of MSC to the adipocyte lineage followed by the terminal differentiation phase characterized by the terminal differentiation of pre-adipocyte into a mature adipocyte (Lowe et al., 2011; Rosen and Spiegelman, 2014). The mature adipocyte acquires various characteristics including lipid transport and synthesis, secretion of adipose specific proteins and insulin sensitivity.

Several signaling pathways are known to regulate the commitment of mesenchymal stem cell precursor to adipocyte, including Insulin like growth factor signaling, WNT signaling pathway, Sonic Hedgehog pathway (Logan and Nusse, 2004), through modulational of various transcription factors including PPARγ and C/EBP family of proteins.

PPAR-γ: THE MASTER REGULATOR OF ADIPOGENESIS

Adipogenic differentiation involves a cascade of events coordinated by several transcription networks, however two key transcription factors crucial for adipogenesis are PPAR γ and C/EBP family members (Hamm et al., 2001; Mueller et al., 2002).

Peroxisome proliferator activated receptors are members of steroid/thyroid hormone receptor gene superfamily. There are three isoforms of PPAR namely PPAR alpha, gamma and delta (Tontonoz and Spiegelman, 2008). PPAR-γ serves as the master regulator of adipogenesis, several studies have demonstrated the requirement of PPAR-γ during both commitment and differentiation phases (Schopfer et al., 2005; Tzameli et al., 2004). All the three isoforms i.e PPARα, PPARδ and PPARγ are expressed during adipogenesis. Recent genome wide studies have indicated that PPARγ and C/EBP regulate the activity of several genes expressed in mature and developing adipocytes (Lefterova et al., 2008; Nielsen et al., 2008) including genes involved in insulin sensitivity, lipogenesis and lipolysis. PPARγ mediated pro adipogenic effects are executed upon its ligands mediated activation, one such set of ligands is thiazoliediones (TZD's), which save as potent agonists for PPARγ (Lehmann et al., 1995). Several studies in animal models have reiterated the central role of PPARγ in adipogenic differentiation. Studies using knock out PPAR-γ mice demonstrated a reduced adipocyte differentiation (Tzameli et al., 2004). The selective deletion of PPARγ is murine adipose tissue led to the less of both brown and white adipocytes (Rosen and Spiegelman, 2014).

WNT AND ADIPOGENESIS

Wingless type MMTV integration site (WNTS) are a family of several glycoproteins which are known to play an essential role in several cellular processes including cell fate determination, proliferation and differentiation (Clevers, 2006). WNT's exert their effect through canonical (β- catenin dependent) and non-canonical (β catenin independent pathways of signaling (Li et al., 2006; Xavier et al., 2014).

The canonical WNT pathway binds to transmembrane frizzled (Frz) receptors, low density lipoprotein receptor related protein 5 or 6 (Lrp 5/6) and intracellular protein of disheveled (DSH) family, which upon activation results in inhibition of another intracellular complex comprising of axin glycogen synthase kinase 3 (GSK3)-β and adenomatous polyposis cote (APC). This results in hypo phosphorylation of β catenin and its translocation into the nucleus where it binds to T cell specific transcription factor (TCF) in order to activate WNT target genes (Bennett et al., 2002; Jones and Jomary, 2002). The non-canonical WNT signaling pathway functions in a β catenin independent manner. The WNT and FZD homologues act through heteromeric GTP binding protein and trigger intracellular calcium release, activating calcineurin and other calcium/calmodulin dependant kinases (Semenov et al., 2007).

Several studies have highlighted the key role of WNT signaling in regulating adipogenesis. WNT's are a key decider in decision of Mesenchymal stem cell precursor's cell fate i.e whether it would commit to oestogenic or adipogenic lineage. Several reports indicate that WNT signaling pathway regulates the mesenchymal stem cell fate by suppressing adipogenesis through the prevention of induction of master regulators PPARγ and C/EBP transcription factors during pread-

ipocyte differentiation (Kang et al., 2007). The endogenous factor WNT10b has been shown to stabilize free cytosolic β catenin, thereby inhibiting adipogenesis (Ross et al., 2000). The expression of WNT 10b is highest during pre-adipocytes and rapidly decreases upon induction of adipocyte differentiation (Ross et al., 2000). A recent study demonstrated the role of WNT6, WNT10a in addition to WNT10b in inhibiting adipogenesis (Cawthorn et al., 2012). A study by Krishnan et al. (2006) reported that the over expression of WNT10b blocks adipogenesis however adding of WNT 10b anti-sera to 3T3-L1 preadipocyte cell lines resulted in promotion of adipogenesis (Krishnan et al., 2006).

WNT SIGNALING AND METABOLIC DISORDERS

Obesity is major contributing factor which preludes to the onset of several chronic metabolic disorders including type 2 diabetes. Therefore it is imperative to understand the intricacies involved in the regulation of adipogenesis including the signaling pathways which are know to regulate this phenomenon. WNT signaling is a crucial regulator of adipocyte differentiation (Welters and Kulkarni, 2008). The importance of WNT signaling pathway in regulation of adipogenesis has come to the forefront as several studies have elucidated that a dysregulation in WNT signaling often preludes to metabolic pathology. Several studies have demonstrated the expression of various components of the WNT signaling pathway members in endocrine cells including human islets and rodent β cell lines (Heller et al., 2003; Hermann et al., 2007). Many components of WNT pathway have been shown to be involved in β cell proliferation, cholesterol metabolism and glucose induced insulin secretion (Fujino et al., 2003; Rulifson et al., 2007).

Polymorphisms in LRP5 and WNT10b have shown to be associated with obesity in the European population (Christodoulides et al., 2006; Guo et al., 2006). Genome wide association studies have identified TCF7L2 as a type diabetes susceptibility gene (Jin, 2008). Furthermore, the key effector of the WNT signaling pathway bipartite transcription factor T cell factor 2 (TCF7L2) polymorphisms have been linked to susceptibility to type 2 diabetes by a number of studies of different ethnicities (Florez, 2007; Weedon, 2007).

CONCLUSION

Extensive and exhaustive research elucidating the role of WNT signaling pathway as a modulator of adipogenesis has generated tremendous interest in the understanding interplay between the WNT signaling cascade components and the triad of diabetes, hyperlipidemia and atherosclerosis. Future studies directed to understand the underlying mechanisms through which WNT signaling regulates adipogenesis and the interplay between the various signaling pathways during adipogenesis would pay the way for future WNT directed therapeutics for metabolic disorders.

ABBREVIATIONS

MSC- Mesenchymal Stem cell, PPAR gamma: Peroxisome proliferator activated receptor.

Competing interests

The authors declare that they have no competing interests.

Open Access

References

Bennett, C.N., Ross, S.E., Longo, K.A., Bajnok, L., Hemati, N., Johnson, K.W., Harrison, S.D., and MacDougald, O.A. (2002). Regulation of Wnt signaling during adipogenesis. *The Journal of biological chemistry* 277, 30998-31004.

Caplan, A.I. (1986). Molecular and cellular differentiation of muscle, cartilage, and bone in the developing limb. *Progress in clinical and biological research* 217b, 307-318.

Cawthorn, W.P., Bree, A.J., Yao, Y., Du, B., Hemati, N., Martinez-Santibanez, G., and MacDougald, O.A. (2012). Wnt6, Wnt10a and Wnt10b inhibit adipogenesis and stimulate osteoblastogenesis through a beta-catenin-dependent mechanism. *Bone* 50, 477-489.

Chamberlain, G., Fox, J., Ashton, B., and Middleton, J. (2007). Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing. *Stem cells (Dayton, Ohio)* 25, 2739-2749.

Christodoulides, C., Lagathu, C., Sethi, J.K., and Vidal-Puig, A. (2009). Adipogenesis and WNT signalling. *Trends in endocrinology and metabolism: TEM* 20, 16-24.

Christodoulides, C., Scarda, A., Granzotto, M., Milan, G., Dalla Nora, E., Keogh, J., De Pergola, G., Stirling, H., Pannacciulli, N., Sethi, J.K., *et al.* (2006). WNT10B mutations in human obesity. *Diabetologia* 49, 678-684.

Clevers, H. (2006). Wnt/beta-catenin signaling in development and disease. *Cell* 127, 469-480.

Farmer, S.R. (2006). Transcriptional control of adipocyte formation. *Cell metabolism* 4, 263-273.

Florez, J.C. (2007). The new type 2 diabetes gene TCF7L2. *Current opinion in clinical nutrition and metabolic care* 10, 391-396.

Fujino, T., Asaba, H., Kang, M.J., Ikeda, Y., Sone, H., Takada, S., Kim, D.H., Ioka, R.X., Ono, M., Tomoyori, H., *et al.* (2003). Low-density lipoprotein receptor-related protein 5 (LRP5) is essential for normal cholesterol metabolism and glucose-induced insulin secretion. *Proceedings of the National Academy of Sciences of the United States of America* 100, 229-234.

Gortmaker, S.L., Swinburn, B.A., Levy, D., Carter, R., Mabry, P.L., Finegood, D.T., Huang, T., Marsh, T., and Moodie, M.L. (2011). Changing the future of obesity: science, policy, and action. *Lancet* 378, 838-847.

Guo, Y.F., Xiong, D.H., Shen, H., Zhao, L.J., Xiao, P., Guo, Y., Wang, W., Yang, T.L., Recker, R.R., and Deng, H.W. (2006). Polymorphisms of the low-density lipoprotein receptor-related protein 5 (LRP5) gene are associated with obesity phenotypes in a large family-based association study. *Journal of medical genetics* 43, 798-803.

Hamm, J.K., Park, B.H., and Farmer, S.R. (2001). A role for C/EBPbeta in regulating peroxisome proliferator-activated receptor gamma activity during adipogenesis in 3T3-L1 preadipocytes. *The Journal of biological chemistry* 276, 18464-18471.

Heller, R.S., Klein, T., Ling, Z., Heimberg, H., Katoh, M., Madsen, O.D., and Serup, P. (2003). Expression of Wnt, Frizzled, sFRP, and DKK genes in adult human pancreas. *Gene expression* 11, 141-147.

Hermann, M., Pirkebner, D., Draxl, A., Berger, P., Untergasser, G., Margreiter, R., and Hengster, P. (2007). Dickkopf-3 is expressed in a subset of adult human pancreatic beta cells. *Histochemistry and cell biology* 127, 513-521.

Jin, T. (2008). The WNT signalling pathway and diabetes mellitus. *Diabetologia* 51, 1771-1780.

Jones, S.E., and Jomary, C. (2002). Secreted Frizzled-related proteins: searching for relationships and patterns. *BioEssays : news and reviews in molecular, cellular and developmental biology* 24, 811-820.

Kahn, B.B., and Flier, J.S. (2000). Obesity and insulin resistance. *The Journal of clinical investigation* 106, 473-481.

Kang, S., Bennett, C.N., Gerin, I., Rapp, L.A., Hankenson, K.D., and Macdougald, O.A. (2007). Wnt signaling stimulates osteoblastogenesis of mesenchymal precursors by suppressing CCAAT/enhancer-binding protein alpha and peroxisome proliferator-activated receptor gamma. *The Journal of biological chemistry* 282, 14515-14524.

Krishnan, V., Bryant, H.U., and Macdougald, O.A. (2006). Regulation of bone mass by Wnt signaling. *The Journal of clinical investigation* 116, 1202-1209.

Lefterova, M.I., Zhang, Y., Steger, D.J., Schupp, M., Schug, J., Cristancho, A., Feng, D., Zhuo, D., Stoeckert, C.J., Jr., Liu, X.S., *et al.* (2008). PPARgamma and C/EBP factors orchestrate adipocyte biology via adjacent binding on a genome-wide scale. *Genes & development* 22, 2941-2952.

Lehmann, J.M., Moore, L.B., Smith-Oliver, T.A., Wilkison, W.O., Willson, T.M., and Kliewer, S.A. (1995). An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *The Journal of biological chemistry* 270, 12953-12956.

Li, F., Chong, Z.Z., and Maiese, K. (2006). Winding through the WNT pathway during cellular development and demise. *Histology and histopathology* 21, 103-124.

Logan, C.Y., and Nusse, R. (2004). The Wnt signaling pathway in development and disease. *Annual review of cell and developmental biology* 20, 781-810.

Lowe, C.E., O'Rahilly, S., and Rochford, J.J. (2011). Adipogenesis at a glance. *Journal of cell science* 124, 2681-2686.

Misra, A., and Shrivastava, U. (2013). Obesity and dyslipidemia in South Asians. *Nutrients* 5, 2708-2733.

Mueller, E., Drori, S., Aiyer, A., Yie, J., Sarraf, P., Chen, H., Hauser, S., Rosen, E.D., Ge, K., Roeder, R.G., *et al.* (2002). Genetic analysis of adipogenesis through peroxisome proliferator-activated receptor gamma isoforms. *The Journal of biological chemistry* 277, 41925-41930.

Nielsen, R., Pedersen, T.A., Hagenbeek, D., Moulos, P., Siersbaek, R., Megens, E., Denissov, S., Borgesen, M., Francoijs, K.J., Mandrup, S., *et al.* (2008). Genome-wide profiling of PPARgamma:RXR and RNA polymerase II occupancy reveals temporal activation of distinct metabolic pathways and changes in RXR dimer composition during adipogenesis. *Genes & development* 22, 2953-2967.

Piersma, A.H., Brockbank, K.G., Ploemacher, R.E., van Vliet, E., Brakel-van Peer, K.M., and Visser, P.J. (1985). Characterization of fibroblastic stromal cells from murine bone marrow. *Experimental hematology* 13, 237-243.

Prestwich, T.C., and Macdougald, O.A. (2007). Wnt/beta-catenin signaling in adipogenesis and metabolism. *Current opinion in cell biology* 19, 612-617.

Rosen, E.D., and Spiegelman, B.M. (2014). What we talk about when we talk about fat. *Cell* 156, 20-44.

Rosen, E.D., Walkey, C.J., Puigserver, P., and Spiegelman, B.M. (2000). Transcriptional regulation of adipogenesis. *Genes & development* 14, 1293-1307.

Ross, S.E., Hemati, N., Longo, K.A., Bennett, C.N., Lucas, P.C., Erickson, R.L., and MacDougald, O.A. (2000). Inhibition of adipogenesis by Wnt signaling. *Science (New York, NY)* 289, 950-953.

Rulifson, I.C., Karnik, S.K., Heiser, P.W., ten Berge, D., Chen, H., Gu, X., Taketo, M.M., Nusse, R., Hebrok, M., and Kim, S.K. (2007). Wnt signaling regulates pancreatic beta cell proliferation. *Proceedings of the National Academy of Sciences of the United States of America* 104, 6247-6252.

Schopfer, F.J., Lin, Y., Baker, P.R., Cui, T., Garcia-Barrio, M., Zhang, J., Chen, K., Chen, Y.E., and Freeman, B.A. (2005). Nitrolinoleic acid: an endogenous peroxisome proliferator-activated receptor gamma ligand. *Proceedings of the National Academy of Sciences of the United States of America* 102, 2340-2345.

Semenov, M.V., Habas, R., Macdonald, B.T., and He, X. (2007). SnapShot: Noncanonical Wnt Signaling Pathways. *Cell* 131, 1378.

Tontonoz, P., and Spiegelman, B.M. (2008). Fat and beyond: the diverse biology of PPARgamma. *Annual review of biochemistry* 77, 289-312.

Tzameli, I., Fang, H., Ollero, M., Shi, H., Hamm, J.K., Kievit, P., Hollenberg, A.N., and Flier, J.S. (2004). Regulated production of a peroxisome proliferator-activated receptor-gamma ligand during an early phase of adipocyte differentiation in 3T3-L1 adipocytes. *The Journal of biological chemistry* 279, 36093-36102.

Weedon, M.N. (2007). The importance of TCF7L2. *Diabetic medicine : a journal of the British Diabetic Association* 24, 1062-1066.

Welters, H.J., and Kulkarni, R.N. (2008). Wnt signaling: relevance to beta-cell biology and diabetes. *Trends in endocrinology and metabolism: TEM* 19, 349-355.

Wu, Z., Rosen, E.D., Brun, R., Hauser, S., Adelmant, G., Troy, A.E., McKeon, C., Darlington, G.J., and Spiegelman, B.M. (1999). Cross-regulation of C/EBP alpha and PPAR gamma controls the transcriptional pathway of adipogenesis and insulin sensitivity. *Molecular cell* 3, 151-158.

Xavier, C.P., Melikova, M., Chuman, Y., Uren, A., Baljinnyam, B., and Rubin, J.S. (2014). Secreted Frizzled-related protein potentiation versus inhibition of Wnt3a/beta-catenin signaling. *Cellular signalling* 26, 94-101.

Cite this article as:

Anil, N. (2014). The Engimatic WNT Signaling and Mesenchymal Stem Cell Adipogenesis: Implications for Metabolic disorders. *Biomedical Research And Therapy, 1*(4):121-125.