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One of the crucial proteins to influence type 2 diabetes: The high mobility group A1

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ABSTRACT

HMGA1 have been shown to transactivate promoters through mechanisms that facilitate the assembly and stability of stereospecific DNA-protein complexes, which promote gene transcription in response to all kinds of signals. Some studies have proved that HMGA1 proteins are relate to insulin resistances and type 2 diabetes. The mechanism can connect with that HMGA1 paticipate in the expression of INSR and IGF-1R; as well as influence insulin production, insulin sensitivity, adipocyte differentiation. Some studies have found that human body can exist in HMGAI-p, the abnomal increasing of HMGAl-p expression can down-regulated the levels of INSR and impair insulin binding. Low-frequency insertion polymorphism IVS5-13insC has been identified and associated with insulin resistance and type 2 diabetes, but conflicting results on diverse ethnic groups have caused difficulty in performing clinical translation of HMGA1 IVS5-13insC genotyping.

KEY WORDS: HMGA1, TYPE 2 DIABETES, INSULIN RESISTANCES, HMGA1-P, HMGA1 IVS5-13INSC

INTRODUCTION

THE STRUCTURE AND FUNCTION OF HMGA1

HMGA1 belongs to the high mobility group (HMG) protein family, comprising all kinds of non-histone proteins(Reeves, 2001). Within this family, the HMGA proteins can prior bind to the minor groove of A/T-rich B-form DNA sequences, because it contain three AT-hook DNA binding motifs. Although HMGA proteins have been predicted no intrinsic transcriptional activity, they could serve as so-called “enhanceosomes” to promote the assembly and stability of stereospecific DNA-protein complexes through transactivate promoters, which facilitate gene transcription in response to a variety of signals(Reeves, 2001, Thanos, *et al.*, 1995).

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HMGA1 orchestrate a large quantity of various transcription factors, such as Sp1, p150, NF-Y, NF-kB, ATF-2, c-Jun, TAF3 at gene promoter and enhancer regions, which participate in gene-specific transcription regulation(Currie, 1997, Leger, *et al.*, 1995, Yie, *et al.*, 1997, X. M. Zhang, *et al.*, 1999(Huth, *et al.*, 1997, Messineo, *et al.*, 2016) .

Thus, it regulates the expression of an impressive number of mammalian genes. Besides, HMGA1 also involved in many other processes, including embryogenesis, differentiation, and neoplastic transformation (Cleynen, *et al.*, 2008, Fedele, *et al.*, 2010, Sgarra, *et al.*, 2004). HMGA1a and HMGA1b were HMGA1 gene encodes spliced isoforms, the latter one lacking 11 amino acids between the first and the second AT-hook motif than the former one(Friedmann, *et al.*, 1993, Nagpal, *et al.*, 1999).

TYPE 2 DIABETES

Type 2 diabetes is one of the major and exacerbating health problems worldwide; type 2 diabetes is shown to affect 490 million in 2030(P. Zhang, *et al.*, 2010). Strong genetic influences and many polymorphisms have been reproducibly associated with type 2 diabetes(Herder, *et al.*, 2011, Voight, *et al.*, 2010). Insulin resistance in muscle, liver, and adipose tissues is a primary characteristic of most patients with type 2 diabetes; as such, these tissues become resistant to endogenous and exogenous insulin. The interaction of insulin with target tissues is mediated by insulin receptor (INSR), a glycoprotein implicated in directing insulin to target cells and initiating cell responses to insulin. Many of these individuals have point mutations in the coding sequence of INSR, the gene that encodes insulin receptor. Receptor abnormalities resulting from defects in the generation of INSR mRNA have been reported in individuals with apparently normal INSR genes, suggesting defects in gene regulation(Goldfine, 1987).

THE RELATIONSHIP BETWEEN HMGA1 AND TYPE 2 DIABETES

HMGA1 proteins are over-expressed in virtually every type of cancer, where their expression levels correlate with tumor malignancy and a poor outcome for patients suffering from that particular type of tumor(De Rosa, *et al.*, 2016, Huso, *et al.*, 2014). But, some studies have also proved that low-expressed HMGA1 proteins are relate to insulin resistances and type 2 diabetes(Aiello, *et al.*, 2010, Foti, *et al.*, 2005) The mechanism can connect with that HMGA1 paticipate in the expression of INSR and isulin-like growth factor 1 receptor (IGF-1R); and influence insulin production, insulin sensitivity, adipocyte differentiation.

HMGA1 POSITIVELY REGULATE THE EXPRESSION OF INSR AND IGF-1R VIA INFLUENCING GENE TRANSCRIPTION

HMGA1 assemble polyprotein-DNA complexes with protein polymer to positively regulate the activity of INSR promoter, which bind to the transcription start site of INSR. Finally, resulting in the positive regulation of INSR expression and insulin signal transduction(Foti, *et al.*, 2005, Kolb, *et al.*, 2007, Paonessa, *et al.*, 2006). Moreover, HMGA1 have also effected on insulin signal transduction through the positive regulation of IGF-1R expression(Aiello, *et al.*, 2010). Foti and his colleagues have found HMGA1 mutation in peripheral blood lymphocyte from subjects with insulin resistance and type 2 diabetes, which result in HMGA1 protein were present at low expression. Restoration of HMGA1 protein expression in subjects' cells enhanced INSR gene transcription, and restored cell-surface insulin receptor protein expression and insulin-binding capacity. These results show that the decrease of HMGA1 is likely to cause insulin resistances and human type 2 diabetes. In animal study, HMGA1 knock-out mice were present at considerably decreased insulin receptor expression in the major targets of insulin action, largely impaired insulin signaling, causing a phenotype characteristic of human type 2 diabetes(Foti, *et al.*, 2005).

HMGA1 CAN FACILITATE INSULIN PRODUCTION VIA REGULATING PDX-1 AND MAFA

Arcidiacono and his colleagues provided evidence that HMGA1 physically interacts with PDX-1 (the pancreatic and duodenal homeobox factor-1) and MafA (V-maf musculoaponeurotic fibrosarcoma oncogene homolog A), two critical transcription factors for insulin gene expression and beta-cell function, both in vitro and in vivo(Hay, *et al.*, 2006). They also show that the over-expression of HMGA1 significantly improves the transactivating activity of PDX-1and MafA on human and mouse insulin promoters, while HMGA1 knockdown considerably decreased this transactivating activity. In addition, they demonstrate that HMGA1 may act as a glucose-sensitive element controlling the transcription of the insulin gene, because high glucose stimulus remarkably increases the binding of HMGA1 to the insulin gene promoter. According to the above analysis, HMGA1, by regulating PDX-1- and MafA-induced transactivation of the insulin gene promoter, is witnessed by affected pancreatic beta-cell function and insulin production(Arcidiacono, *et al.*, 2014).

HMGA1 PARTICIPATE IN THE REGULATION OF INSULIN HYPERSENSITIVITY TO ADAPT IMPAIRED GLUCOSE TOLERANCE

Due to the restriction of medical ethics, we could not do an in-depth study for finite patients with HMGA1 mutation. Thus, some researchers carry on depth studies via animal model. A study showed that the expression of insulin receptor is off by 90% and appear to hyperglycemia simultaneously in Hmga1-knockout mice. But, in Hmga1-knockout mice peripheral insulin hypersensitivity paradoxically coexisted with a condition of impaired glucose tolerance and overt diabetes. Moreover, the expression of the insulin-regulatable glucose transporter 4 (Glut4) was increased in muscular tissue (Foti, *et al.*, 2005). We could not precisely explain that the sensitivity to insulin emerged discrepancy between peripheral tissues from human and mouse.

This phenomenon showed that the existence of molecular adaptation mechanisms in Hmga1-knockout mice. Two systems are now considered to explain this phenomenon.

1. **The cAMP-HMGA1-RBP4 system:** adipose tissue can release of the adipose-derived serum RBP4, which its amounts have a negative correlation with the expression of Glut4 (Yang, *et al.*, 2005). RBP4-knockout mice appear to insulin hypersensitivity. Provided exogenous RBP4 or over-expression RBP4 in body can induce insulin resistance. However, HMGA1-knockout mice really existed the decreasing of RBP4 mRNA and peripheral blood RBP4 levels. Then, exogenous RBP4 were corrected the enhancing of Glut4 in the muscle tissue of HMGA1-knockout mice, and correspondently, the unusual high effect of insulin reduces blood sugar was declined remarkably. In the study on wild-type mice, found that glucagon can stimulate the expression of HMGA1 and RBP4, whereas this situation could not emerge on HMGA1-knockout mice. Thus, HMGA1 plays an direct role in RBP4 promoter to paticipate in pancreatic glucagon stimulate the expression of RBP4. Because pancreatic glucagon release is regulated by the cAMP pathway, hence, thinking of that cAMP is regulatory factor for HMGA1 and RBP4 gene(Chiefari, *et al.*, 2009).
2. **(2)The HMGA1-IGF-I/IGFBP System:** Numerous results of experimental and clinical studies evidence that IGF-I plays a vital role in normal carbohydrate metabolism(Woods, *et al.*, 2000, Yakar, *et al.*, 2001). The IGF-binding proteins 1 (IGFBP1) and 3 (IGFBP3), two major members of the IGF-binding protein superfamily, by influencing both the bioavailability and distribution of IGF-I in the extracellular environment, hold a crucial position in IGF-I ligand-receptor interactions, (Baxter, 2000, Clemmons, 1997). They demonstrated that IGF-I's bioactivity was increased, but levels of IGFBP1 and IGFBP3 are considerably decreased in Hmga1-knockout mice. They hypothesize that, under certain adverse metabolic conditions, functional inactivation of HMGA1, by adversely affecting the expression of both IGFBP proteins, may reflect an adaptive mechanism to increase IGF-1's bioactivity, ensuring recruitment of Glut4 to muscle plasma membrane and tissue glucose disposal. However, the precise mechanisms by which these compensatory circuits of glucose uptake are activated and provide signals for the translocation remain to be fully characterized and elucidated (Iiritano, *et al.*, 2012).

HMGA1 CAN INVOLVE IN FORMING INSULIN RESISTANCE VIA INHIBITING ADIPOCYTE DIFFERENTIATION

The importance of poorly adipocyte differentiated for development and progression of insulin resistance is witnessed (Gustafson, *et al.*, 2015). HMGA1 can promote adipocyte differentiation, enhance the ability to store fat, improve body of insulin sensitivity (Melillo, *et al.*, 2001). Two transcriptional factor, CCAAT/enhancer-binding proteinβ (C/EBPβ) and retinoblastoma protein (RB), been considered plays an important role in the process of adipocyte differentiation(Chen, *et al.*, 1996). A study found that HMGA1 is pivotal protein in adipocyte differentiation due to it involve in the formation of the RB-C/EBPβ complex. They also found that Hmga1-knockout embryonic stem cells difficult to undergo this process. This provided a result that HMGA1 may plays a crucial role in adipocyte differentiation, in other words, pool adipocyte differentiation induce insulin resistance and type 2 diabetes may relate to the abnormal decreasing of HMGA1(Esposito, *et al.*, 2009).

However, in the other study, they generated aP2-HMGA1 transgenic mice which over-express HMGA1 in adipose tissues to discover the function of HMGA1 in vivo. They found that the genes involved in adipocyte differentiation were down-regulated and preadipocyte marker genes were up-regulated in white (WAT) and brown (BAT) adipose tissue from aP2-HMGA1 transgenic mice. So, over-expression of HMGA1 lead to impaired WAT and BAT creation through inhibiting the adipogenic process and increasing adipose precursor. Over-expression of HMGA1 can decrease body-weight gain, reduce fat mass, but improve insulin sensitivity and glucose tolerance when fed a high-fat diet. Interest-

ingly, this provide an evidence that aP2-HMGA1 transgenic mice were protected against diet-induced obesity and insulin resistances (Arce-Cerezo, *et al.*, 2015).

THE ABNOMAL EXPRESSION OF HMGA1-P CAN CAUSE TYPE 2 DIABETES VIA COMPETING WITH HMGA1

Some studies have found that human body can exist in HMGAl-pseudogene (HMGA1-p), the abnomal increasing of HMGAl-p expression can have effect on the expression of HMGA1 protein(Esposito, *et al.*, 2015, Esposito, *et al.*, 2014). Targeted knockdown of HMGA1-p in patient lymphoblasts can results in reciprocally increasing HMGA1 mRNA stability and expression levels with a parallel correction in cell-surface INSR expression and insulin binding. A recombinant plasmid carrying the entire HMGA1-p was generated and transiently transfected into cultured human HeLa cells, caused decrease in HMGA1 mRNA levels and influence INSR gene transcription. When silent HMGAl-p expressed, the level of HMGA1 mRNA was restored, besides, the expression of INSR mRNA and protein were up-regulated. Under normal circumstances, αCPl interacts with the region of HMGA13'-UTR C-rich repeats, linked to stabilization of HMGA1 mRNA. Due to the 3'terminal portion of HMGA1-p maintains extensive sequence homology with the HMGA1 3'-UTR. HMGA1-p can result in increased HMGA1 mRNA degradation, decreased HMGA1 protein expression, resulted in the deceasing of INSR expression by competing for αCP1(Chiefari, *et al.*, 2010).

HMGA1 IVS5-13INSC ASSOCIATED WITH INSULIN RESISTANCE AND TYPE 2 DIABETES

Strong genetic influences and many polymorphisms have been reproducibly associated with type 2 diabetes. IVS5-13insC (c.136-14_136-13insC) is present at position 13 of HMGA1 exon 6; Low-frequency insertion polymorphism IVS5-13insC has been identified and associated with insulin resistance and associated with insulin resistance and type 2 diabetes among individuals of white European ancestry and Chinese populations(Chiefari, *et al.*, 2011, Liu, *et al.*, 2012, Lv, *et al.*, 2015).

However, no similar association is observed in another study involving Caucasians and populations of African and Hispanic descent(Karnes, *et al.*, 2013, Marquez, *et al.*, 2012, Pullinger, *et al.*, 2014). Furthermore, conflicting results regarding the association of HMGA1 with type 2 diabetes and insufficient data on diverse ethnic groups have caused difficulty in performing clinical translation of HMGA1 IVS5-13insC genotyping.

Results regarding the functional effect of the HMGA1 IVS5-13insC variant are also contradictory. On the one hand, HMGA1 and INSR expressions decrease in diabetic carriers of IVS5-13insC compared with those of wild-type diabetic and non-diabetic patients(Chiefari, *et al.*, 2011). INSR protein expression and insulin-binding capacity are also restored in lymphoblasts obtained from diabetic IVS5-13insC carriers through HMGA1 DNA transfection. On the other hand, IVS5-13insC does not affect HMGA1 or INSR expression in adipose tissues of normoglycemic patients(Marquez, *et al.*, 2012) and also have not the association with the susceptibility of DR in the Chinese T2DM cohort(Lv, *et al.*, 2016).

Genome-wide association studies (GWAS) on patients with type 2 diabetes have identified associations between polymorphisms and mutations in some genes(Chiefari, *et al.*, 2013). These genes have been regarded as potential type 2 diabetes risk factors. However, current GWAS fail to detect an association between the HMGA1 variant IVS5-13insC and the presence of type 2 diabetes. To better understand, some studies that include GWAS datasets will help determine whether the IVS5-13insC shows a consistent association with type 2 diabetes. However, the direct mechanism by which this variant affects mRNA expression or amino acid sequence remains unclear.

As we have shown above, HMGA1 mainly act as an architectural transcription factor involved in glucose homeostasis. Thus, many factors can induce type 2 diabetes by affecting its function of transcription regulation. They are some examples for that:

Disrupt Self-regulatory mechanism: The HMGA1 gene been regulated by an octamer motif, which was identified as an important element of transcriptional regulation. Based on the present study revealing that Oct-1 and Oct-2 is crucial in modulating HMGA1 gene and protein expression(Chiefari, *et al.*, 2013). However, HMGA1 can also transactivate octamer transcription factor promoter, providing evidence for the existence of an auto-regulatory circuit in which HMGA1 activates its own transcription. If this mechanism is broken, sush as Oct-1 gene variants, can also result in type2 diabetes(Ng, *et al.*, 2010).

Disrupt indirect regulatory mechanism: (1)HMGA1 and PKCε: Incubation of skeletal muscle cell with FFA for 6 h reduced HMGA1 protein exprerssion. But, in the presence of eV1, a PKCε translocation inhibitor peptide, neither reduction nor phosphorylation of HMGA1 protein could be observed. These results suggest that FFA-induced PKCε inhibits insulin gene transcription through the impairment of HMGA1(Dey, *et al.*, 2007). Some studies indicate that SFA's inhibitory effect on INSR expression is mediated through the kinase independent phosphorylation of PKCε, then migrates to the nuclear region and phosphorylates HMGA1 that retards its migration to INSR promoter which adversely affects INSR β mRNA expression. FRL, purified from

the leaves of Hibiscus mutabilis, can permit HMGA1 to activate INSR β promoter in skeletal muscle cells, which improved INSR expression deficiency though blocking PKCε activation(Dasgupta, *et al.*, 2011, Gogoi, *et al.*, 2014). This report can link up HMGA1 with overweight is the risk factors for diabetes. **(2) HMGA1 and NPM1:** A research focus on two human genes, the INSR genes and the IGFBP1 genes, whose expression is directly regulated by HMGA1. A study demonstrated that occupancy of their promoters by HMGA1 was NPM1-dependent, however, decrease in NPM1 abundance is followed by increase in the occupancy of promoter DNA by HMGA1, can resulting in increased promoter activity(Arnoldo, *et al.*, 2015). Thus, we put a hypothesis that free HMGA1 can up-regulate NPM1 expression in turn, resulting in decreased promoter activity. But, if NPM1 delete or reduce excessively, broken this regulatory mechanism, can affect normal function of HMGA1.

FUTURE PROSPECTS

HMGAl plays a crucial role in blood sugar balance as a structural transcription factor. HMGA1 can cause insulin resistances and type 2 diabetes via changing it function. This is novel opinion for the pathogenesis of type 2 diabetes nearly 10 years. However, the exact biological mechanism underlying the association between the HMGA1 gene and risk of type 2 diabetes remains uncertain. Thus, further more accurate studies on HMGA1 are warranted to clarify in diabetes pathogenesis.

We believe that an individual with the decreasing of HMGA1 has specific clinical implications. First of all, the presence of the levels of HMGA1 may predict responses to therapy. Type 2 diabetes treatment is largely empirical and the prediction of specific responses to a therapeutic agent in any patient is difficult(Karnes, *et al.*, 2013). Patients with type 2 diabetes and different pathogeny may respond differently to specific therapies, such as an insulin sensitizer, because HMGA1 decrease or variant defines a specific defect that decreases insulin receptor concentrations and insulin resistance. Second, individuals possessing functional HMGA1 and type 2 diabetes may have different clinical courses from other patients with type 2 diabetes, including differences in the development of complications. Third, the search for new therapies for type 2 diabetes can include agents that upregulate HMGA1 expression. Furthermore, HMGA1 can be regarded as a novel target of gene therapy for type 2 diabetes and insulin resistance.

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