AN EVOLUTIONARY PERSPECTIVE ON ADIPONECTIN AND INSULIN GENE PROMOTERS

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Abstract

Insulin, discovered in 1921 by Nicolae Paulescu, and adiponectin, discovered in 1995 by Yuji Matsuzawa's and two other groups, are two important molecules related to the maintenance of human energy homeostasis. The close relationship of these two hormones in the development of metabolic pathology (obesity, metabolic syndrome, type 2 diabetes mellitus) prompted us to use a bioinformatic approach in order to better understand the architecture of their gene promoters. In this study, a comprehensive analysis was undertaken for adiponectin (ADIPOQ) and insulin (INS) gene promoter sequences from 7 species. In our approach we used 14 promoter sequences (7 promoters for each gene) from HomoloGene (NCBI). In order to examine the structural particularities of ADIPOQ and INS gene promoters, we used two-dimensional image-based patterns obtained through Kappa Index of Coincidence (Kappa IC) and (C+G)% values. We observed that C+G content variations of ADIPOQ promoter correlates with body mass, whereas high Kappa IC values of the INS gene promoter appear to be correlated with brain size.

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Key words: ADIPOQ gene promoter, INS gene promoter, body mass, brain mass, BMI, evolution

Introduction

In our society, obesity is a direct consequence of lifestyle, environmental exposuers, and genetic predisposition (1-3). It is currently associated with a considerable number of pathological conditions, such as type 2 diabetes mellitus (T2DM), cardiovascular disease, arthritis and other various complications (1,4).

Adipose tissue is the major „warehouse” for triglycerides and a main link in the energy balance mechanism. Generally, adipose tissue mass increases when energy intake exceeds energy consumption. Thus, the adipose tissue stands to be as an active and dynamic endocrine subsystem that produces a number of signaling proteins known as adipokines, which affect the function of adjacent and/or distant organs in health and disease (5-8). Examples of „the rapidly expanding family of adipokines” (9) include adipisin, leptin, adiponectin, apelin, chemerin, interleukin-6 (IL-6), IL-10, plasminogen activator inhibitor-1 (PAI-1), retinol-binding protein 4 (RBP4), tumor necrosis factor-alpha (TNF-α) and visfatin (8-10). The most

abundant adipokine is adiponectin (a relatively large 244-amino-acid-long polypeptide) which is found in human serum at high concentrations (between 2-20 µg/mL) and is inversely correlated with body mass index (BMI), T2DM, atherogenesis and cancerogenesis (11-15). In the bloodstream, adiponectin circulates in different forms, such as trimeric, hexameric and higher order complexes (16). Adiponectin treatment is able to counteract T2DM and atherosclerosis as well as other pathological states (17-25). Compared to normal individuals in which adiponectin is inversely related to glucose and insulin, the obese patients exhibit decreased concentrations of adiponectin (26,27). We suggest that an overview from an evolutionary perspective of insulin and adiponectin may open new avenues for addressing the issues in both obesity and T2DM.

In the present study, we tried to observe two correlations in several species: (i) between body mass (not to be confused with BMI) and ADIPOQ gene promoters, and (ii) between brain mass and INS gene promoters. In order to understand their cor-

relation at the genetic level, we used our own original method based on Kappa index of coincidence, as previously published (28).

In our approach we used 14 promoter sequences (7 promoters for each gene) from HomoloGene (29). We used 500 bases upstream of ADIPOQ gene and INS gene from *Homo sapiens* (NT_005612.16), *P. troglodytes* (NW_003456895.1), *C. lupus* (NW_003726120.1), *B. taurus* (NW_003103812.1), *M. musculus* (NW_003103812.1), *R. norvegicus* (NW_047356.1) and *G. galus* (NW_001471743.2). We used Visual Basic to develop a software program for promoter analysis - called PromKappa (Fig. 1). In this method we have used sliding window approach for reading two types of values: Kappa IC and (C+G)%.

We observed that C+G content variations of ADIPOQ promoter seem to be correlated with body mass. On the other hand, high Kappa IC values of INS gene promoter appear to be correlated with brain size. In this case, high Kappa IC values are caused by long C+G based homopolymers. Thus the correlation

Figure 1. Prom Kappa Software (Promoter analysis by Kappa).

is made between long C+G based homopolymers and brain size (Fig. 2). Moreover, from a genetic point of view, one of the genome areas associated with susceptibility for T2DM includes adiponectin (30,31). Several missense mutations of adiponectin are also associated with T2DM (32,33). Clinically, adiponectin serum levels are reduced in obese or T2DM patients and are especially low in obese individuals with high visceral fat content (34-36). Furthermore, it was observed that anti-diabetic drugs cause an increase in adiponectin levels (37). Adiponectin receptors (Adip-R1 and Adip-R2) were found to be expressed in the proopiomelanocortin and neuropeptide tyrosine (NPY) neurons in the arcuate nucleus, thus, linking adiponectin to an even more active role in the central regulation of energy intake and consumption (38).

Interestingly, some studies suggest that T2DM in octogenarians is associated with decreased low molecular weight of adiponectin (39). Adiponectin molecules self-associate into larger structures. In this process of self-association, three adiponectin molecules bind together to form a trimer, units that continue to self-associate in hexamers or dodecamers (40). In human serum, the relative levels of adiponectin higher-order structures (high-molecular weight forms) seem to be increased in females. In relation to glucose homeostasis, the high-molecular weight form of adiponectin appears to be more biologically active and was associated with a lower risk of T2DM (41,42).

Other studies link obesity (through low adiponectin levels) to an elevated risk of breast, colorectal or prostate cancer (43-46). Also, adiponectin can reduce cell migration and invasion in cancer (47). Nevertheless, the biochemical mechanisms behind the action of adiponectin in cancer prevention are unknown. Although the beneficial implications of adiponectin start getting increasingly clearer, the clinical trials regarding an adiponectin therapy in humans has yet to be expected. The administration of adiponectin in mouse has already shown promising effects (48-50).

Figure 2. Promoter patterns of ADIPOQ and INS gene promoters. Each promoter pattern is composed of vertically aligned clusters of Kappa IC (y-axis) and GC% (x-axis) values. The center of weight for each pattern is represented by a black circle. Both values have a range between 1 and 100.

Conclusion

The role of adiponectin in developing T2DM prompted many studies over the last 10 years. In this paper, a comprehensive analysis was undertaken for ADIPOQ and INS promoter sequences from 7 species. In our approach we used 14 promoter sequences (7 promoters for each gene) from HomoloGene (NCBI). In order to examine the structural particularities of ADIPOQ and INS gene promoters, we used two-dimensional image-based patterns obtained through Kappa Index of Coincidence (Kappa IC) and (C+G)% values. In our analysis we observed that C+G content variations of ADIPOQ promoter correlates with body mass. On the other hand, high Kappa IC values of INS gene promoter appear to be correlated with brain size. Our data also suggests that C+G content variations of ADIPOQ promoter correlates with body mass. How interaction between insulin and adiponectin could explain the actual cardiometabolic pathologies remains to be *Danced round* using metabolomic, interactomic and genomic approaches.

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