METABOLISM CLINICAL AND EXPERIMENTAL 60 (2011) 747–748

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Editorial

# Clusterin (apolipoprotein J): wither link with diabetes and cardiometabolic risk?

Clusterin (also known as *apolipoprotein J; Apo J; SP-40, 40; sulfated glycoprotein-2; SGP-2*), was first isolated in 1983 [1]. Clusterin was named on the basis of the initial observation that it has the ability to cause aggregation of suspended cells (primarily Sertoli cells) into "clusters" [1,2]. Clusterin in humans was described for the first time in 1989 as a "complement lysis inhibitor"; and 1 year later, de Silva et al demonstrated that clusterin has the same sequence with apolipoprotein J [3] and that it constitutes a separate subclass of high-density lipoprotein (HDL), the apo J–HDL, with a vertical gradient centrifugation density that ranges from the values of HDL-2 up to the values of very high-density lipoprotein [4]. Clusterin is encoded in all tissues as a single gene, but it is transcribed into 3 messenger RNA isoforms (isoforms 1, 2, and 11036) that are subsequently translated into a wide variety of proteins [5]. These isoforms are grouped, according to their localization, into nCLU (nuclear fraction of clusterin) and sCLU (secreted fraction of clusterin).

Although a PubMed search for clusterin/apolipoprotein J yields 1538 publications, 135 of which are review articles, our understanding on the role of clusterin in humans continues to evolve. Clusterin has been proposed to be associated with a variety of biological processes, such as: promotion of erythrocyte aggregation, attenuation of complement activity, reverse lipid transportation, sperm maturation, and regulation of apoptosis. Clusterin's speculated role in complement regulation and lipid metabolism inevitably attracted the attention of investigators studying inflammation and lipid metabolism and the pathophysiologic sequel of these conditions, namely, cancer, atherosclerosis, and, more recently, metabolic syndrome and diabetes mellitus.

Clusterin's association with inflammation and lipid transportation makes it reasonable to speculate that it could also be associated with cardiometabolic disease. Studies in rodents have proposed that clusterin may play a role in vascular smooth muscle migration and proliferation [6,7] and have suggested that clusterin might exert a cardioprotective action not only during acute ischemia but also in the remodeling phase [6]. In humans, only one observational case-control study is available to date; and it demonstrates that both the lytic components of complement (C3d and C5b-9) and the complement inhibitor clusterin were up-regulated in specimens of atherosclerotic and degenerated aortic valves, with activated complement predominating over its inhibitors [7]. Laboratory and epidemiologic studies have shown that lower circulating clusterin levels are associated with prostate cancer [8,9], gastric carcinoma [10], breast cancer [11], as well as colon [12,13], cervical [14,15], and ovarian [16] cancers.

In the area of the metabolic syndrome/diabetes, which frequently underlies the development of both cardiovascular disease and certain malignancies, research evidence is coming essentially from observational/epidemiology studies. A small cross-sectional study demonstrated that circulating clusterin levels are similar in males and females [17] and that there is a positive correlation between clusterin and apo A, apo B, total cholesterol, low-density lipoprotein, HDL, and years of documented diabetes mellitus, in contrast to a negative correlation with apo E. Finally, healthy individuals had statistically significantly higher serum clusterin levels in comparison to subjects with diabetes and to patients with myocardial infarction, chronic coronary artery disease, as well as diabetes plus chronic coronary artery disease [17]. A subsequent study of similar size confirmed that clusterin levels are increased in diabetic patients when compared with controls [18], whereas in a more in-depth study examining clusterin levels in the HDL fraction of lean insulin-sensitive vs lean insulin-resistant and obese insulin-resistant middle-aged subjects, it was demonstrated that HDL clusterin is significantly decreased in the lean insulin-resistant group and is even lower in obese insulin-resistant subjects when compared with the lean insulin-sensitive group [19]. Thus, secreted circulating clusterin may be positively associated, whereas HDL clusterin may be negatively associated, with insulin resistance, metabolic syndrome, and diabetes.

In this issue of the journal, Daimon et al [20] examine the relationship between clusterin gene polymorphisms and diabetes, demonstrating a significant association between the rs2279590 clusterin gene polymorphism and the prevalence of type 2 diabetes mellitus. This polymorphism was also positively associated with higher body mass index, homeostasis model assessment–R, and homeostasis model assessment–$\beta$ levels. Although these data need to be confirmed and the generalizability of this study beyond the Japanese population needs to be established, this is the first study that shows a significant association between clusterin gene polymorphisms, insulin resistance, and diabetes. In addition

to replication studies that need to confirm such associations in other populations, observational studies linking this polymorphism with altered levels of circulating secreted and/or HDL clusterin as well as mechanistic interventional studies are needed in our effort to reach a better understanding of the role clusterin and/or specific clusterin fractions play in diabetes and the metabolic syndrome.

In summary, clusterin is a molecule that has been proposed to be associated with diabetes and the metabolic syndrome as well as their sequelae including the development of cardiovascular disease and certain malignancies. It would also be of importance to explore a potential molecular link between clusterin and leptin biology, as clusterin has been proposed to function as a leptin-binding protein [21]. Further observational epidemiologic, mechanistic, and interventional studies are required to further elucidate the role of clusterin in human biology including the metabolic syndrome, diabetes, cardiovascular diseases, and malignancies.

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0026-0495/$ – see front matter


doi:10.1016/j.metabol.2010.12.013

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