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COMMENTARY

A commentary on Association of adiponectin polymorphism with cord blood adiponectin concentrations and intrauterine growth

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Since its discovery back in the beginning of the 90s,[1] adiponectin—an exclusive product of adipocytes abundantly secreted into circulation—has attracted much attention owing to its close association with insulin sensitivity,[2] body fat[3] and its role in the etiopathogenesis of type 2 diabetes, as well as its potential therapeutic action. To date, a considerable number of studies have been published aiming to elucidate the possible involvement of adiponectin in several different pathologies that share insulin resistance as the common background (hypertension, dyslipidemia, cardiovascular disease, polycystic ovary syndrome and fatty liver disease among others) and adiponectin physiological behavior throughout life.

A good share of the adiponectin studies investigated the associations among variations in the adiponectin gene (*ADIPOQ*)—in particular, single-nucleotide polymorphisms (SNPs), adiponectin levels, metabolic features and the risk of developing non-communicable chronic diseases in a variety of ethnical backgrounds. Of note, two SNPs in the promoter region of the *ADIPOQ* gene (rs17300539 and rs266729) presenting linkage disequilibrium have been associated with adiponectinemia and obesity risk in some populations.[4]

Abnormal fetal growth, either restriction or increase of weight for gestational age, had been linked to variations in adiponectin levels, insulin resistance, obesity and increased risk of type 2 diabetes later in life. There is a direct relationship between adiponectin and fetal growth as insulin is a key regulator of intrauterine growth and adiponectin, on its turn, closely affects tissue insulin sensitivity. For this reason it is rational to investigate if SNPs associated with adiponectin levels in adult life can also have a role in prenatal growth and later life consequences.

In this context the present study by Saito *et al.*[5] offers an important contribution to elucidate the prenatal growth role of *ADIPOQ* gene SNPs frequently found in the Japanese population. They analyzed the association of these SNPs with birth size and cord blood adiponectin levels in Japanese neonates born adequate for gestational age (AGA). In an earlier work, this research team demonstrated that serum adiponectin levels in the first day of life were significantly higher in AGA neonates than in those born with small for gestational age (SGA) birth weight.[6] These previous data likely reinforced the potential role of adiponectin in prenatal growth. On the other hand, it is also possible that the lower levels of adiponectin found in SGA neonates as observed in that study are just a consequence of fetal growth impairment.

An important contribution of the present study by Saito *et al.* is to demonstrate a significant association of the SNP rs266729 (−11377C>G) with variations in birth size and cord blood adiponectin levels. Subjects carrying the polymorphic G allele presented higher cord blood adiponectin levels and greater birth weight s.d. score than those homozygous for the C allele. These data contribute to the knowledge that the influence of the SNP rs266729 starts early in life. To date only one previous study had demonstrated a significant association between ADPOQ SNPs, prenatal growth and postnatal adiponectin levels. In that study, evaluating a cohort of Brazilian subjects from birth to adult life, Bueno *et al.*[7] observed that the variant A allele of the SNP rs17300539, which is located very close to the SNP rs266729, was associated with increased birth weight and adiponectin levels in adult life.

It is important to point out that the influence of the SNP rs266729 on adiponectin levels may vary among subjects from different ethnic backgrounds. In European subjects the polymorphic G allele was shown to be associated with lower adiponectinemia in adults and obese children, although *in vitro* assays failed to show its functionality.[4,8] These differences may occur even within subjects of Asian ancestry, as demonstrated by a recent genomewide association study in Korean healthy adult subjects. In this population the same allele, −11377G, was not found to be associated with higher adiponectin levels.[9]

The finding that a SNP in the *ADIPOQ* gene is associated with adiponectin levels and influences body adiposity at birth reinforces the role of adiponectin in fetal development. It is tempting to continuously evaluate the cohort evaluated by Saito *et al.* to observe whether or not these associations remain after birth. If this effect lasts, these Japanese subjects carrying the polymorphic −11377G allele would present higher adiponectinemia and consequently lower cardiometabolic risk throughout life. However, a recent study in Chinese Han subjects observed exactly the

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opposite association. In that study, homozygosity for the same G allele was associated with a twofold-increased risk of ischemic stroke.[10] Thus it appears that there are some 'paradoxes' yet to be elucidated in the field of adiponectin SNP studies. When facing these intriguing findings, a wise old saying comes to my mind: 'The end of one work is only the beginning of another'.

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