GENETIC AND EPIGENETIC STUDIES OF DIABETES AND DIABETIC NEPHROPATHY WITH FOCUS ON THE IGF-IGFBP AXIS

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av
Tianwei Gu

Huvudhandledare:  Fakultetsopponent:
Professor Kerstin Brismar Professor Peter Bang
Institutionen för molekylär medicin och kirugi Institutionen för klinisk och experimentell
Karolinska Institutet medicin

Bihandledare:  Betygsämnd:
Associate Professor Harvest F Gu Professor Anna Krook
Institutionen för molekylär medicin och kirugi Institutionen för fysiologi och farmakologi
Karolinska Institutet Karolinska Institutet

Professor Dan Holmberg Institutionen för experimentell medicinsk
Institutionen för medicinsk vetenskap
vetenskap
Lunds Universitet

Associate Professor Leonid Padyukov Institutionen för medicin, centrum för
Institutionen för molekylär medicin molekylär medicin
Karolinska Institutet

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Abstract

Diabetes and diabetic nephropathy (DN) are complex diseases reflecting a complex interplay between genetic and non-genetic factors. The insulin-like growth factor (IGF)-IGF binding protein (IGFBP) axis plays an important role in the development of diabetes and DN. Recent reports have demonstrated that genetic polymorphisms in this axis are associated with diabetes and DN. However, the information of epigenetic study is very limited. In this study, we selected four genes from this axis including IGF1, IGF2, IGFBP1 and IGF2BP2 to evaluate their genetic and epigenetic associations with diabetes and DN. In parallel, we analyzed the serum protein levels.

SNP rs35767 in the IGF1 gene promoter region has been reported to be associated with insulin resistance and circulating IGF-I levels. In Study I, we analyzed IGF1 DNA methylation levels at CpG sites in the promoter region including this SNP and measured serum IGF-I concentration in Swedish subjects with normal glucose tolerance (NGT) or type 2 diabetes (T2D). Data suggested that increased DNA methylation in the gene promoter and decreased circulating IGF-I levels are associated with T2D.

IGFBP-1 is produced in liver and mainly regulated by insulin. Clinical observations have demonstrated that high levels of circulating IGFBP-1 are associated with T1D, while low serum levels are associated with the risk of T2D. There is a CpG island at the promoter and 5'-untranslated region (5'-UTR) of the IGFBP1 gene. We analyzed IGFBP1 DNA methylation levels in Swedish T2D patients (Study II) and T1D patients with or without DN (Study III). Results demonstrated that IGFBP1 DNA methylation levels were decreased in T1D patients but increased in T2D patients in comparison with NGT subjects. Furthermore, decreased and increased IGFBP-1 serum levels were respectively associated with T2D and T1D.

The IGF2BP2 gene is located on chromosome 3q27.2 within a region linked to diabetes and DN. The protein encoded IGF2BP2 binds to 5'-UTR of the imprinting IGF2 gene, which is located on chromosome 11p15.5. In Study IV, we genotyped SNPs rs10770125 (A/G) and rs4402960 (G/T) in the IGF2 and IGF2BP2 genes respectively. Diabetes patients with or without DN and NGT subjects from GoKinD, Czech and Swedish populations were enrolled in this study. Data showed that the IGF2BP2 polymorphism rs4402960 was associated with T2D. This IGF2BP2 polymorphism and rs10770125 in the IGF2 gene were found to be associated with DN in male T1D patients.

In conclusion, our studies provide evidence that the IGF1, IGF2, IGFBP1 and IGF2BP2 genes have genetic and epigenetic effects in diabetes and DN. To better understand the importance of our findings, further investigations of tissue specific DNA methylation levels and their impacts on translated proteins are needed.

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