S-B36

Genetic Variations in Soluble Epoxide Hydrolase and the Long-term Graft Function in Kidney Transplantation

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Background : Endothelial dysfunction plays key role in the development and progression of chronic allograft dysfunction. Epoxyeicosatrienoic acids (EET) are endothelium-derived hyperpolarizing factors and contribute to renal and cardiovascular protective actions by vascular dilation, anti-inflammatory effects, and profibrinolytic effects. EETs are metabolized to less active or inactive dihydroxyeicosatrienoic acids by soluble epoxy hydrolase. The genetic variations of soluble epoxide hydrolase (EPHX2) may alter levels of expression of EPHX2 contributing to biological activity of EETs. We studied the association of genetic variations in EPHX2 with kidney allograft dysfunction.

Methods and Results : One hundred eighty kidney transplant donor-recipient pairs were recruited. The polymorphisms of exon 8 (R287Q) and 3'UTR (rs104203 A/G) were genotyped using Taqman method. Patients were 43.0±13.7 years old at the time of operation and followed for 84.7±53.1 months. Mean estimated GFR (eGFR) at the last follow up was 51.0±25.0 mL/min. Of 180 transplant recipients, 35 (19.8%) had allograft dysfunction with eGFR less than 30 mL/min. Allele frequencies of 2 polymorphisms were in Hardy-Weinberg equilibrium. GG, GA, and AA genotype frequencies in R287Q were 60.9%, 35.8%, and 3.3% in recipients, respectively, and 63.3%, 31.1%, and 5.6% in donors. No significant association between R287Q variant allele and risk of deteriorated allograft function was observed (G/G, 49.0±26.9 mL/min vs. A/G or A/A, 53.7±21.6 mL/min, p=0.222). But rs104203 variant allele in recipients had higher final eGFR (A/A, 44.7±28.2 mL/min vs. A/G or G/G, 53.8±23.0 mL/min, p=0.026) and was associated with significantly lower risk for the progression to chronic kidney disease (CKD) stage IV or V (eGFR less than 30 mL/min, p=0.010). In multivariate analysis, rs104203 variant allele was associated with the lower risk for the decreased eGFR less than 30 mL/min (OR =0.36, CI 0.17-0.79). On the contrary, rs104203 variant allele in donors had no impact on the final eGFR (p=0.673) and the progression to CKD stage IV or V (p=0.401).

Conclusion : Our results suggest that the presence of rs104203 polymorphism variant allele in EPHX2 is associated with kidney allograft dysfunction.