Diabetic retinopathy progresses from mild non-proliferative abnormalities to proliferative retinopathy and is considered to develop as a consequence of long duration of poor glycemic control as well as due to the existence of hypertension and several genetic factors. Early studies of identical twins with diabetes mellitus suggest familial clustering of diabetic retinopathy. Furthermore, the Diabetes Control and Complications Trial (DCCT) suggests that the severity of diabetic retinopathy is influenced by familial factors, possibly genetic background (1). According to these evidence, researchers have been searching for the genes responsible for retinopathy. Generally, genes which encode factors involved in the pathogenesis of diabetic retinopathy are considered as candidates. The interaction of advanced glycation end products (AGEs) with the receptor for AGE (RAGE) is one of the plausible mechanisms for the development of retinopathy. The AGE-modified proteins accumulate in tissues with increasing age; this process is accelerated in patients with diabetes. AGEs are known to impair cellular function on binding to their specific cellular surface receptors such as RAGE. RAGE in truncated form has a molecular weight of 35 kD and is a multiligand receptor which belongs to immunoglobulin superfamily. The gene for RAGE is located on chromosome 6p21.3 near the HLA locus. The interaction of AGEs with RAGE alters intracellular signaling, gene expression, release of pro-inflammatory molecules and free radicals that contribute to the pathology of diabetic retinopathy. Thus, the genes encoding the RAGE protein are considered as plausible candidate genes susceptible to diabetic retinopathy. To date, at least 30 polymorphisms of RAGE gene have been reported and the association between diabetic retinopathy and the polymorphism of RAGE gene has been studied. Hudson et al have identified 8 novel polymorphisms in the RAGE promoter and have shown an increased frequency of the C allele at –429 T/C functional promoter site in patients with type 1 diabetes with retinopathy compared with those without retinopathy (2). Furthermore, the G82S polymorphism in exon 3 of the RAGE gene with the G82S occurring in the AGE binding domain has been associated with diabetic retinopathy in type 2 diabetic Asian Indian patients (3). However, others do not confirm these associations of these functional –429 T/C and –374 T/A gene polymorphisms with diabetic retinopathy in both Caucasians and Chinese with type 2 diabetes mellitus (4, 5). Furthermore, RAGE G82S polymorphism is not associated with diabetic retinopathy in Chinese type 2 diabetic patients (6). As compared with diabetic retinopathy, the functional –374 T/A RAGE gene polymorphism is associated with proteinuria and cardiovascular disease in type 1 diabetic patients (7). In this issue, Yoshioka et al have also reported that there is no association between C1704T and G82S polymorphisms of the RAGE gene and diabetic retinopathy in Japanese patients with type 2 diabetes mellitus (8).

The question is why there is such variability in searching the susceptible genes of diabetic retinopathy. The differences in race, type of diabetes, other characteristics of selected patients, specificity of control subjects in case-control studies, and sample size might be confounders among studies. The RAGE gene might not have a strong impact on the development of the diabetic retinopathy in Asian patients with type 2 diabetes mellitus as compared with Caucasians. Additionally, an early epidemiological study indicated that the accumulated incidence of retinopathy increases according to the duration of diabetes and that about 75% of patients with diabetes has proliferative retinopathy after 40 years of diabetes (9). In contrast to retinopathy, the cumulative incidence of diabetic nephropathy rises to a peak of approximately 30%, at 20 years after diagnosis of diabetes (9). These observations suggest that the genetic factors related to the development of diabetic retinopathy might have a weaker impact than diabetic nephropathy. A large scale prospective cohort study and/or the synergistic combination of conventional approaches with new emerging technologies (e.g. biochips) will be key factors to identify the genetic background of diabetic retinopathy.

Atsunori KASHIWAGI and Shin-ichi ARAKI
Department of Medicine, Shiga University of Medical Science,
Seta, Otsu, Shiga 520-2192
References


