Abstract

Effect of smoking on the association between the *GPR141*-rs2392510 and periodontitis

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The previous Genome-Wide Association Study (GWAS) of Japanese patients with periodontitis revealed that *GPR141* (rs2392510) was a suggestive disease-related gene. *GPR141* has also been shown to interact with smoking history in the gene-environmental relationship in the study, but its function has not been clarified.

In this study, (1) 115 patients with periodontitis were recruited in order to analyze the relationship between genotype (AA, AG, GG) of *GPR141* (rs2392510) and clinical information, (2) localization of *GPR141* with immunofluorescence staining was performed on gingival tissue harvested at the time of periodontal surgery from six periodontitis patients, (3) effect of *P. gingivalis* (*P. g*) LPS, nicotine, and *P. g* LPS + nicotine stimulation, on *GPR141*, IL-8, and MCP-1 gene expression was evaluated with the isolated monocytes from peripheral blood of three generally healthy non-smokers with one of each GPR141 genotype, (4) fluorescent immunostaining was performed on the cultured THP-1 cells when stimulated with LPS, nicotine or *P. g* LPS + nicotine to evaluate the *GPR141*-positive cell rate.

It was indicated that (1) % of the sites with probing pocket depth (PPD)≧ of 4 ㎜ was significantly higher [54.3% (SD: 24.3), 36.5% (26.4)] and the total tooth number was significantly smaller [19.9 (SD 5.4), 24.2 (5.4)] in AA than those in AG + GG in the smokers, (2) *GPR141*-positive cells were found mainly in the inflammatory cell infiltrates under the oral epithelium, (3) *GPR141* gene expression of monocytes isolated from AA were significantly down-regulated with the *P. g* LPS stimulation, while no such significant changes were observed in those from AG + GG, and gene expression of IL-8 and MCP-1 were significantly up-regulated with the *P. g* LPS and *P. g* LPS + nicotine stimulation in the monocytes of AA, (4) the *GPR141*-positive cell rate was significantly decreased with the *P. g* LPS, nicotine, and P. g LPS + nicotine stimulation compared to the unstimulated condition.

These results indicated that *GPR141* protein-positive cells gathered in the

inflammatory cell infiltrates of the periodontal lesion and the allele AA might increase the susceptibility to periodontitis in smokers leading to the enhanced risk of the deepening periodontal pocket and tooth loss. It was also indicated that increases of *GPR141* production in the lesion of AA with *P. g* infection and nicotine may lead to enhancing the development of inflammation via increased migration of monocytes and neutrophils due to increased production of MCP-1 and IL-8.

In summary, *GPR141* is suggested to be downregulated by *P. g* LPS and nicotine and a potential risk factor for periodontitis. The decreased expression of rs2392510 in AA may increase the susceptibility to periodontitis.