Table 3 Target genotypes and study population in association with periodontal disease and smoking

Genotypes	Subjects	Main findings	Articles
IL-1A -889, IL-1B +3954 (originally described as +3953)	134 subjects, USA	The polymorphic IL-1 gene cluster was associated with severity of periodontitis only in non-smokers.	59
IL-1A -889, IL-1B +3954 (originally described as +3953)	28 African-American and 7 Caucasian-American families (early onset periodontitis affected and unaffected subjects), USA	IL-1ß disequilibrium with EOP was found both in smokers and non-smokers.	57
IL-1A -889	46 patients and 12 controls, UK	The carriage of allele 2 was associated with an increase in IL-l α protein levels, especially in non-smokers, while heavy smokers showed reduced levels of IL-lα protein, regardless of genotype.	28
IL-1A -4845, IL-1B -3954	295 Caucasians, Australia	A relationship was observed between the IL-1-positive genotype and increased mean probing pocket depth in non-smokers more than 50 years of age. IL-1 genotype-positive smokers had an increase in the number of probing depths ≥3.5 mm.	56
IL-1A +4845, IL-B +3954	90 patients (non- or former smokers), USA	IL-1 genotype-positive non-smokers or former light smokers were at increased odds of having moderate-to-severe periodontal disease compared to IL-1 genotype-negative patients. The presence of both former moderate smoking history and IL-1-positive genotype showed a lower likelihood of developing the disease when compared to those with presence of only one of the risk factors.	60
IL-1A -889, IL-1B +3954, IL-1RN	154 Caucasians, Germany	Severity of periodontitis was associated with the composite genotype of IL-1α/1β in smokers, while no differences were found in genotype-negative subjects, irrespective of their smoking status.	62
IL-1A -889, IL-1B +3954, IL-1B -511	1085 Caucasians, Germany	An increased risk of periodontal disease and tooth loss was observed for IL-1 genotype-positive smokers.	61, 63, 64
IL-1A -889 IL-1B +3954	330 patients and 101 controls, Chile	The association between positive genotype and periodontitis was independent of smoking status.	58
IL-6 -174	155 patients and 54 controls, Brazil	An association between the G-genotype and periodontal status was observed only in non-smokers.	65
IL-10 -1087	60 patients and 39 controls, Sweden	An association between the GG genotype and periodontal status was more conspicuous in non-smokers.	66
Vitamin D receptor -1056 Taq-I	303 patients and 231 controls, UK	Vitamin D receptor Taq-I TT polymorphism was moderately associated with both the presence and progression of periodontitis in smokers.	70
FcγRIIIb	164 subjects aged 70 years old, Japan	An association between smoking and periodontal disease progression in elderly people with FcγRIIIb-NA2 polymorphism.	68
FcγRIIa	422 Caucasians, USA	FcγRIIa-H/H131 genotype may be associated with chronic periodontitis risk in smokers.	69
FcγRIIIa -158V/F, FcγRIIIb -NA1/NA2	1083 Caucasians, Germany	Smokers show a significantly increased attachment loss in the presence of FcγRIIIb-NA2 allele. The different genotypes show no differences in non-smokers.	63
IFNGR1	62 patients and 56 controls, Norway	In combination with smoking, IFNGR1 was significantly associated with periodontitis.	67
NAT2 -T341C, -G590A, G857A MPO G-463[a]	1083 Caucasians, Germany	Smokers with the high activity variant of NAT 2 and MPO are at an increased risk of periodontitis.	63

IL: interleukin, FcγR: Fcγ receptor, IFNGR1: interferon gamma receptor 1, NAT: N-acetyltransferase, MPO: myeloperoxidase

associated with both the presence and progression of periodontitis in smokers [70]. Gene polymorphisms for enzymes that can metabolize smoking-derived substances may contribute to individual susceptibility to the risk of periodontitis among smokers. Subjects with the polymorphic cytochrome P450 1A1 M2 allele and glutathione S-transferase M1 allele exhibited an increased risk of periodontitis [71].

Conclusions

The process of periodontal disease is such that a microbial challenge induces a host response, which may result in connective tissue and alveolar bone destruction. Most findings support that smoking modulates the destruction of the periodontium through different pathways: microcirculatory and host immune systems, connective tissue, and bone metabolism. Although smokers exhibit an

increased burden of inflammatory responses to microbial challenges compared to non-smokers, substantial problems still persists with respect to the accuracy of measurements, and particularly, the sampling of many subjects. Limited evidences are available regarding the effects of quitting smoking on pathophysiological changes in periodontal tissue.

At present, gene-smoking relationships in periodontal disease are suggestive. The reported gene-smoking relationships in periodontal disease should be carefully interpreted in two ways. First is the uncertainty of the relationship because of methodological limitations such as employment of subjects in a specific race, small sample size, and lack of detailed history of smoking and possible confounders. Further studies with adequate statistical power and small biases would be required to clarify the relationship. Furthermore, it remains unclear whether genetic susceptibility to periodontal disease is influenced by exposure to smoking or the effect of smoking on periodontal disease is influenced by genetic susceptibility. The second issue is an ethical problem. If a smoker with positive genotypes associated with inflammatory cytokines is proven to be at a high risk of periodontal disease, the evidence is so strong that the smoker should be encouraged to quit smoking. In contrast, however, the evidence may cause a smoker with negative genotypes to avoid quitting smoking, thereby causing fatal diseases. Within such limitations, gene-environment relationship studies possibly provide valuable insights into the pathogenesis of complex periodontal diseases and are expected to contribute to prevent the disease through personalized recommendation and targeted intervention in dental public and clinical programs.

Employment of molecular techniques may play a key role in further elucidation of mechanisms linking smoking and periodontal destruction, the direct relationship as environmental factors and indirect relationship through genetic factors.

Acknowledgements
TH is supported by a Grant-in-Aid for Cancer Research (17-1), Health and Labor Sciences Research Grants for Clinical Cancer Research (H19-010), Comprehensive Research on Cardiovascular and Life-Style Related Diseases (H19-007) from the Ministry of Health, Labor, and Welfare, Japan, and Grant-in-Aid for Exploratory Research from the Japan Society for the Promotion of Science.

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Authors' contributions
MO evaluated the literature and drafted the manuscript. TH conceived the idea for the review and helped draft the manuscript. Both authors participated in the design and coordination of the review. They also read and approved the final version of the manuscript.

Competing interests
The authors declare that they have no competing interests.

Received: 17 October 2009
Accepted: 20 February 2010 Published: 20 February 2010

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doi:10.1186/1617-9625-8-4
Cite this article as: Ojima and Hanioka: **Destructive effects of smoking on molecular and genetic factors of periodontal disease.** *Tobacco Induced Diseases* 2010 **8**:4.