学位論文内容の要旨
Abstract of the dissertation

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学位論文題名
The title of the doctoral dissertation

The Association of Thyroglobulin Single Nucleotide Polymorphism with Miniature Dachshunds-Specific Inflammatory Colorectal Polyps and its Involvement in Interleukin-6 Amplifier Induced Chronic Inflammation

(ミニチュアダックスフンドに特異的な炎症性結直腸ポリープに関連するサイログロブリンの一塩基多型とインターロイキン 6 増幅回路に誘導される慢性炎症への関与)

Inflammatory colorectal polyp (ICRP) of Miniature Dachshund (MD) is a novel inflammatory bowel disease (IBD) characterized by granulomatous inflammation consisting neutrophil infiltration and goblet cell hyperplasia in the colorectal region with an unknown pathogenesis. Whole-exome sequencing revealed that *TG* c.4567C>T and FBN1 c.1205C>T (p.P402L) are MD specific single nucleotide polymorphisms (SNP), but only thyroglobulin (*TG*) was found to be significantly different between disease-control groups in our cohort ($P = 0.0221$). Mechanistic analysis showed that *TG* increased the activation of the IL-6 amplifier, which is an enhanced-*NF-κB* activation in nonimmune cells in the presence of a simultaneous activation of *NF-κB* and *STAT3* and is a fundamental machinery of various inflammatory diseases in patients and animal models. Indeed, *TG* treatment increased *NF-κB*-mediated IL-6 expression, while *TG* deficient reduced it at lease in vitro. Moreover, we showed that *NF-κB* and *STAT3* were more activated in intestine samples with risk allele comparing to those with non-risk allele. Although systemic expression of *TG* was unable to be detected, local expression of *TG* was increased in normal intestine samples with risk allele. Thus, these results suggest that regional increase of *TG* expression in intestine induces chronic inflammation via the activation of the IL-6 amplifier in MDs, which may also be important in human IBD patients with concurrent thyroidal disease.