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

博士の専攻分野の名称 : 博士(獣医学)

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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.