Human IL-1 Alpha Conditional Transgenic Mice Mimic Autoinflammatory Syndromes In Human.

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Introduction:
Recently, IL-1 is implicated in the pathogenesis of autoinflammatory syndromes, which characterized by rash, fever, systemic polyarthritis and neurological comorbidity. Recently, IL-1 becomes noticed now as a therapeutic target of adult onset still’s disease and macrophage activation syndrome. To date, animal model of adult onset “IL-1 disease” has not been reported. Herein, we newly established IL-1alpha transgenic mice with conditional regulation of IL-1alpha overexpression, which mimicked adult onset IL-1 disease in humans. The purpose of the present study is to clarify the pathology of adult onset IL-1 disease through these mice.

Methods:
Human IL1alpha (hIL1alpha) conditional transgenic (cTg) mice were generated as loxP-neomycin resistant gene (Neo)-polyA-loxP-hIL1alpha sequence under an beta-actin promotor in a C57BL/6 background. In non-inducing condition, Neo was expressed without hIL1alpha-expression, whereas in inducing condition in the presence of Cre, Neo-polyA sequence was popped out, and hIL1alpha overexpression was induced. We crossed inducible MxCreTg mice with hIL1alphacTg to yield MxCre/hIL1alphacTg. PolyIpolyC (pI-pC) was administered to 8 week-old cTg mice to activate Mx promotor. The mice were sacrificed two weeks after pI-pC administration, and the severity of arthritis was evaluated using arthritis score, followed by a histological examination.

Results:
Two weeks after pI-pC administration, hIL1alphacTg mice developed large joint arthritis in upper and lower limbs, and its incidence was 100%. Histopathologically, loss of cartilage, bony erosion, and the formation of pannus-like tissues were observed in all cTg mice. The level of transgene-derived hIL1alpha in blood was significantly elevated. The number of white blood cells and platelets were significantly elevated, in contrast, red blood cell count and hemoglobin level were decreased. The levels of IL-6, TNF, and leukemia inhibitory factor (LIF) was significantly elevated. The bone mineral density of the femur was significantly reduced. Flowcytometric analysis revealed that the proportion of Mac1+Gr1+ was significantly elevated in joint fluid and bone marrow.

Discussion: We generated a mouse model of autoinflammatory syndromes in which systemic inflammatory arthritis was intentionally induced under a control of pI-pC administration. The incidence of large joint arthritis was 100% even in a relatively arthritis-resistant C57BL/6 background. These mice are recognized as a useful tool for better understanding of adult onset IL-1 disease.

Significance:
We developed a new mouse arthritis model, which exhibits characteristic features of human IL-1 disease such as large joint arthritis. Our animal model is considered a useful tool to develop new therapeutic strategy for IL-1 disease.

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References: