INFLAMMATORY SKIN DISEASES (OTHER THAN ATOPIC DERMATITIS & PSORIASIS)

NOD2-RELATED SYSTEMIC AUTOINFLAMMATORY GRANULOMATOSIS, BLAU SYNDROME

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Blau syndrome, or early-onset sacrcoidosis, is a hereditary juvenile-onset systemic granulomatosis. Clinical symptoms appear before the age of 4 years and mainly affect the skin, joints, and eyes. The symptoms are progressive and cause severe complications, such as joint destruction and blindness. Although TNF-α antagonists are effective for controlling some symptoms, there is no specific curative treatment at present. Heterozygous mutations of NOD2 was identified as responsible for the onset. NOD2 protein is an intracellular pathogen recognition receptor, the ligand of which is muramyl dipeptide (MDP) found in bacterial cell walls. On recognition of MDP, NOD2 leads to activation of NF-κB pathway, thereby causing upregulation of proinflammatory cytokines. However, the details regarding the molecular mechanisms by which disease-associated mutant NOD2 leads to autoinflammation and granuloma formation are still unclear.
Since we reported a first sporadic case with NOD2 mutation from a patient to be diagnosed as early-onset sacrcoidosis, we identified about 50 patients in Japan with a confirmed genetic diagnosis, including 6 familial cases.
To clarify the relation between disease associated-mutant NOD2 and the inflammatory response, we established induced pluripotent stem (iPS) cells from Blau syndrome patients. Functional analyses using these iPS-derived monocytic cells suggested IFNγ is a critical mediator for onset of the inflammatory manifestations in this disease. Through the up-regulation of NOD2, IFNγ induced ligand-independent NF-κB activation and proinflammatory cytokine production in iPS-derived macrophages with disease associated mutation. This experimental observation may be supported with the clinical observation that BCG vaccination was sometimes associated with the disease onset, since IFNγ is a major cytokine associated with BCG-mediated immune responses.
Our data support the significance of autoinflammation in the pathophysiology, providing an opportunity for probing therapeutic targets of Blau syndrome.