

COMMENTARY

Autoinflammatory disease, Nakajo-Nishimura syndrome and further perspective

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One focus of *Trends in Immunotherapy* is autoinflammatory disease. In the past, papers have introduced various autoinflammatory diseases^[1,2]. Recently, the concept of these diseases has expanded, and intractable psoriasis, severe acne, and similar related diseases are occasionally included in this disease entity^[3-7].

Among autoinflammatory diseases, Nakajo-Nishimura syndrome has some intriguing aspects, such as gene mutation, treatment options, and the presence of antinuclear antibodies in sera^[1,8]. This syndrome is a hereditary proteasome dysfunction and was initially believed to exist only in a few areas of Japan^[8-11]. However, this disease and related syndrome have also been reported internationally^[12,13].

Mutations of proteasome subunit β -type 8 (PSMB8) have been detected in autoinflammatory diseases characterized by systemic relapsing inflammations and progressive wasting, such as Nakajo-Nishimura syndrome and chronic atypical neutrophilic dermatosis with elevated temperature—also known as chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome and related nomenclature^[8-13]. Kanazawa *et al.* have commented on the validity of this disease nomenclature^[14]. Subsequently, identification of mostly biallelic variants of other proteasome subunits and chaperone genes, such as PSMB10, leading to loss of function of the proteasome, has been defined as proteasome-associated autoinflammatory syndrome (PRAAS)^[15-18].

In *Nature Communications*, Kanazawa *et al.* recently reported a PRAAS with immunodeficiency, which causes different proteasome dysfunction due to a new heterozygous gene mutation, with analysis of a valuable mouse model^[19]. This study reported a new heterozygous missense variant of the PSMB9 proteasome subunit gene observed in two unrelated Japanese infants, which resulted in amino acid substitution of the glycine (G) by aspartic acid (D) at position 156 of the encoded protein β 1i. The reported patients experienced pulmonary hypertension and immunodeficiency, which were distinct from typical PRAAS symptoms. In these patients, the ubiquitin accumulation was

barely detectable. Kanazawa and Kaisho developed a mouse model of the heterozygous human genetic variant (PsmB9G156D/+) and these mice recapitulated several important disease phenotypes of human patients. In the molecular structure, PSMB9 G156D interfered with the β -ring- β -ring interaction of the wild type protein that is necessary for 20S proteasome formation. They proposed a new entity, proteasome-associated autoinflammatory syndrome with immunodeficiency (PRAAS-ID), which is distinct from PRAAS^[19].

The discovery of similar pathologies, which are caused by several abnormalities in proteasome subunits, in human diseases and the reproducibility of several of these pathologies in mouse models are vital in elucidating autoinflammatory diseases, and open new horizons for research.

Recently, the concept of interferonopathy has been proposed in undetermined inflammatory diseases, and the importance of type 1 interferons (IFN) has been noted^[20]. It is expected that future research will develop and accumulate.

Conflict of interest

No conflict of interest was declared by the author.

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