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Genetic interferonopathies: An overview

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A B S T R A C T

Interferonopathies comprise an expanding group of monogenic diseases characterised by disturbance of the homeostatic control of interferon (IFN)-mediated immune responses. Although differing in the degree of phenotypic expression and severity, the clinical presentation of these diseases shows a considerable degree of overlap, reflecting their common pathogenetic mechanisms. Increased understanding of the molecular basis of these Mendelian disorders has led to the identification of targeted therapies for these diseases, which could also be of potential relevance for non-genetic IFN-mediated diseases such as systemic lupus erythematosus and juvenile dermatomyositis. In this paper, we summarise the current knowledge of the molecular basis, clinical features and the treatment available for monogenic interferonopathies.

Introduction

Interferons (IFNs) are signalling proteins that are synthesised and released by immune host cells in response to the presence of several pathogens such as viruses, bacteria, parasites and tumour cells [1–5]. The induction, transmission and resolution of the IFN-mediated immune response is tightly regulated and finely tuned by opposing augmenting and suppressive signals induced by host factors [1–5]. These signals rapidly mobilise an effective antimicrobial response against the invading

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pathogen, while restraining the magnitude of the response to avoid excessive inflammatory responses, thus limiting host injury [1–5]. The interferonopathies are an expanding group of complex genetic disorders characterised by disturbance of the homeostatic control of these IFN-mediated immune responses (Fig. 1) [1–5]. Although differing in the degree of phenotypic expression and severity, the clinical presentation of these diseases shows a considerable degree of overlap, reflecting their common pathogenetic mechanisms [1–5]. This paper summarises the current knowledge of the molecular basis, clinical features and treatments available for monogenic interferonopathies (Table 1).

Proteasome-associated autoinflammatory syndromes

Autoinflammatory diseases resulting from dysfunctional proteasomes are termed as proteasome-associated autoinflammatory syndromes (PRAAS) [6–11]. PRAAS include the Japanese autoinflammatory syndrome with lipodystrophy (JASL), Nakajo-Nishimura syndrome (NNS), joint contractures, muscular atrophy, microcytic anaemia, panniculitis-associated lipodystrophy (JMP) syndrome and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome [6–13]. Despite the different nomenclature, they probably represent the same spectrum of disease rather than discrete disease entities; therefore, unsurprisingly, they have many overlapping clinical features, all of which result from loss-of-function mutations in genes encoding proteasome components and causing proteasome malfunction and proteostasis (proteome homeostasis: the process by which cells control the abundance and folding of the proteome) [6–11].

Aetiology/pathogenesis

Proteasome, thymoproteasome and immunoproteasome

The 26S proteasome complex is an evolutionarily conserved cylindrical organelle that plays an essential role in ubiquitin-tagged protein degradation and is expressed in all body cells [6–11]. It comprises a single catalytic 20S proteasome with 19S regulatory components attached to the ends [6–11]. The 20S proteasome is formed by 14 α subunits and 14 β subunits, in which β1 (coded by the *PSMB6* gene), β2 (coded by *PSMB7* gene), and β5 (coded by *PSMB5* gene) subunits possess protease activities [6–11]. The standard constitutive proteasome is present in most eukaryotic cells, and the thymoproteasome is a specific proteasome found only in the thymus [6–11]. The immunoproteasome refers to a special type of proteasome, composed of β1i (coded by *PSMB9*), β2i (coded by *PSMB10*) and β5i (coded by *PSMB8*) subunits, instead of the β1, β2 and β5 subunits (respectively) of the standard proteasome [6–11]. The immunoproteasome-specific β subunits are induced by IFN-γ stimulation [6–11]. The β5i subunit possesses strong chymotrypsin-like activity, and β1i and β2i subunits have caspase- and trypsin-like activities, respectively [14]. The immunoproteasome efficiently generates peptides that are presented by MHC class I and degradation of oxidised proteins to maintain cellular homeostasis [8,15,16].

Genetic mutations causing PRAAS

NNS, JMP and CANDLE syndromes are caused by mutations in the *PSMB8* gene, although different regions of this gene are involved in the different subtypes [6–11]. Agarwal et al. found a homozygous missense mutation, c.C224T, in the *PSMB8* gene resulting in a p.T75M change in JMP patients [9]. Arima et al. reported that the causal mutation of NNS is a p.G201V mutation in *PSMB8* exon 5 [11]; Liu et al. described one patient with the CANDLE syndrome that had a homozygous nonsense mutation at position 405 resulting in a C to A change with a protein truncation [8]. Four other patients were homozygous, and two others had a heterozygous missense mutation at c.C224T [8].

Recently, however, it has become clear that CANDLE is a genetically heterogeneous recessive disease with new mutations in various combinations described in 8 patients (including a digenic disease model) involving the following genes: the *PSMA3* gene encoding α7; *PSMB4* encoding β7; *PSMB9* encoding β1i; novel mutations in *PSMB8* and in the proteasome maturation protein (*POMP*) gene [16]. One patient had compound heterozygous *PSMB4* gene mutations: c.G(-9)A in the 5′ UTR, and a 9-bp in-frame deletion

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