Incontinentia pigmenti (IP) is a severe X-linked genodermatosis with an incidence of between 1/10,000 and 1/100,000 that presents almost exclusively in females, as male cases die in utero before the second trimester. In affected females the disorder is highly variable in presentation but always associated with skin defects. Typically, IP is characterized by four distinct dermatological stages that begin within two weeks after birth with blisters and an inflammatory response, accompanied by a massive eosinophilic granulocyte infiltration into the epidermis (Stage I /Vesicular Stage). Subsequently, verrucous hyperkeratotic lesions develop (Stage II/Verrucous Stage) and disappear over time, leaving behind areas of hyperpigmentation due to melanin accumulation (Stage III/Hyperpigmented Stage).

In addition to skin signs, IP patients can also suffer from ophthalmologic, odontological or neurological problems. A very striking feature of IP pathology is the extensive X inactivation skewing that is observed in peripheral blood cells of female patients. This skewing reflects an efficient mechanism of counter-selection against cells carrying the mutated X chromosome.

The gene responsible for IP was originally mapped to an interval of about 2Mb distal to the colour vision locus in Xq28. Among the putative candidate genes was NEMO. It was among the first genes to be sequenced because of an apparent increased sensitivity of IP embryonic fibroblasts to apoptosis. Quite remarkably, the analysis of a large collection of patients showed that 70-80% of them carried the same complex rearrangement of the NEMO locus. This rearrangement induces the excision of the region between two MER67B repeated sequences located upstream of exon 4 and downstream of exon 10 respectively.

The excision may be favoured by the presence of a NEMO pseudogene (ΔNEMO) located 22 kB 3’ apart from NEMO in a reverse orientation, and which contains a highly homologous sequence (more than 99%) to NEMO exons 4-10. Indeed, both NEMO and ΔNEMO appear inserted into a similar genomic domain of approximately 35.5 kb.

The recurrent NEMO rearrangement results in the synthesis of a truncated 133 amino acids protein (corresponding to exons 1-3), which is devoid of activity but still able to interact with the IKKs. A lack of NF-κB activation in IP patients carrying this rearrangement was demonstrated by studying foetus-derived primary fibroblasts: these cells are unresponsive to all tested NF-κB-activating stimuli, they do not show degradation of the IkB molecules when stimulated, and they are very sensitive to TNF-induced apoptosis. Then, amorphic mutations in NEMO gene are responsible for IP with lethality in males. Interestingly, hypomorphic mutations in NEMO gene arise in a complex phenotype in boys, OL-EDA-ID, associating osteopetrosis (O), Lymphoedema (L), anhidrotic ectodermal dysplasia (EDA) and immunodeficiency. We identified in two unrelated boys with OL-EDA-ID the same mutation, which consisted in a change of the stop codon for a tryptophane. This generates a protein with additional 27 irrelevant amino acids in the C-terminal part of NEMO. We demonstrated that in contrast to IP cells, NF-κB activation in OL-EDA-ID cells is impaired but not abolished. This small tail of amino acids destabilizes the NEMO protein and then alters NF-κB activation. Mutations in the NEMO gene were also described in boys with EDA-ID without osteopetrosis and lymphoedema as well as in boys with immunodeficiency without EDA. Importantly, all the EDA-ID mutations lead to reduced but not abolished NF-κB activation, explaining why affected male patients survive. Moreover, since their single X chromosome carries the mutated gene, the physiological consequences of NF-κB dysfunction in humans can be directly observed. In contrast, female patients carrying the same NEMO mutations remain healthy or exhibit very mild signs of IP.
Unusually severe life threatening and recurrent bacterial infections of the lower respiratory tract, skin, soft tissues, bones and gastrointestinal tract, as well as meningitis and septicaemia in early childhood characterize the immunodeficiency that affects male patients with EDA-ID. The causative pathogens are most often Gram-positive bacteria (Streptococcus pneumoniae and S. aureus), followed by Gram-negative bacteria (Pseudomonas spp. and Haemophilus influenzae) and mycobacteria.

The high sensitivity of EDA-ID patients to infection results from an impaired cellular response of peripheral blood lymphocytes to LPS, IL-1β, IL-18, TNF-α and CD40L. Other NF-κB-dependent pathways are likely to be affected as well. Indeed, NEMO-dependent NF-κB activation is important for the signalling pathways downstream of Toll receptors (Tlr) and these receptors represent major pathogen sensors.

A consistent feature of EDA-ID pathology is impaired antibody response to polysaccharide antigens. Most patients also exhibit hypogammaglobulinaemia with low serum IgG levels. The levels of other immunoglobulin isotypes (IgA, IgM and IgE) can vary but numerous EDA–ID patients have been described with elevated serum IgM levels (the so-called “hyper-IgM” phenotype). This syndrome can be caused by the inability of their B cells to switch in response to CD40 ligand (CD40L). Alternatively, the immunoglobulin switch can be normal but defective proliferation and differentiation generates a «hyper-IgM-like» phenotype.

In addition to these B-cell abnormalities, impaired NK activity has also been reported in several patients. In contrast, patients with EDA–ID have a normal T-cell proliferation index in response to mitogens and antigens.

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