A new form of Anhidrotic Ectodermal Dysplasia with Immunodeficiency caused by abolished Store-Operated Ca2+ Entry

BACKGROUND: Calcium signaling is fundamental to many cellular processes. An important pathway for increasing intracellular Ca2+ levels is store-operated Ca2+ entry (SOCE) regulated by stromal interaction molecule (STIM1)-2, and Ca2+-channels formed by ORAI1-3 proteins. Mutations in the ORAI1 and STIM1 genes that abolish SOCE cause a combined immunodeficiency (CID) syndrome that is accompanied by autoimmune and noninfectious syndromes.

CASE REPORT: Here we present patients with Anhidrotic Ectodermal Dysplasia with Immunodeficiency (EDA-ID) caused by novel homozygous p.V181SfsX8, p.L194P, and p.G98R mutations in the ORAI1 gene (Fig 1) that suppressed ORAI1 protein expression and SOCE in the patients' lymphocytes and fibroblasts (Fig 2&3). A unifying feature of patients with null mutations in ORAI1 is EDA. Anhidrosis was present in patients P1 to P4 and confirmed by pilocarpin iontophoresis. Patients had dry and exfoliate skin, and they showed signs of heat intolerance and thermoregulatory instability characterized by several attacks of facial flushing accompanied by tachycardia, tachypnea, and hypotension. A skin biopsy specimen showed the presence of eccrine sweat glands in the dermis demonstrating that anhidrosis is not due to a defect in sweat gland development. Recently, we reported that sweat glands require SOCE for opening of the Ca2+-activated channel TMEM16A and thus chloride secretion and sweat production, pointing that anhidrosis in ORAI1-deficient patients could be functional (Fig 4). ORAI1-deficient patients had severe enamel defects diagnosed as hypocalcified amelogenesis imperfecta type III (Fig 5). In severe patients with EDA-ID caused by NF-kB signaling defects also have a tooth defect, which is characterized by hypoplastic enamel morphology and thus is manifested from the enamel defects in ORAI1-deficient patients. ORAI1-deficient patients showed thin and brittle hair.

RESULTS: Patients had dry/exfoliative skin, thin/brittle hair, heat intolerance/thermoregulatory instability, attacks of facial flushing, tachycardia, tachypnea, hypotension, anhidrosis, impaired eccrine sweat glands due to Ca2+-activated chloride channel TMEM16A dysfunction, severe enamel defects. Conventional T/B cells development and numbers were preserved compared to their

CONCLUSION: We propose that mutations in ORAI1 that abolish SOCE constitute a new form of EDA-ID and are an important differential diagnosis of EDA-ID caused by defects in NF-kB signaling.