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Genetic Variants of Store-Operated Channels and Human Diseases

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The functional role of Ca^{2+} influx in non-excitable cells was elusive for many years. In 1986, Prof. Putney [1] firstly proposed the concept of capacitative Ca^{2+} channels (also called store-operated channel). In his model, agonist-mediated empty of intracellular Ca^{2+} stores triggers the activation of calcium channels. In 1992, a series of patch clamp experiments by Hoth and Penner [2] identified a Ca^{2+}-selective current that was evoked by intracellular stores. This calcium channel was named "Ca^{2+} release-activated Ca^{2+} (CRAC) channels". However, there were two fundamental questions in the field. First, how is calcium ion detected within the calcium store? Second, what is the gene of store-operated calcium channel? By using siRNA screening, *STIM1*, an intracellular calcium sensor, was found in 2005 [3,4]. Furthermore, the molecular identification of store-operated calcium channel was emerged based on the studies from two laboratories. Feske et al. [5] identified *ORAI1* as the key protein responsible for store-mediated Ca^{2+} influx. The loss of function mutation of *ORAI1* causes human severe combined immune deficiency (SCID). Approaches of genome-wide RNAi screens in Drosophila cells, Vig et al. [6], identified *CRACM1* (*CRAC modulators 1*) as a regulator in CRAC currents. Using in vitro cell-based studies, Parekh's group provided evidence that Ca^{2+} entry through store-operated calcium channels triggered the generation of the pro-inflammatory signals-LTC_4 [7,8]. Animal models revealed the significant roles of STIM1 [9], *ORAI1/CRACM1* in mast cell degranulation [10] and cancer cell development [11,12].

The first study of a genetic defection *ORAI1* in humans was reported by Feske et al. [5], when a mutation (asparagine 91 to tryptophan) in exon 1 of the *ORAI1* gene was detected in SCID patients. Due to the genetic mutation, lymphocytes failed to evoke store-operated calcium signals-mediated cytokines production. Feske's group further identified three mutations (A103E, L194P and A88SfsX25) in *ORAI1* gene that resulted in loss of channel functions [13]. Recently, genetic polymorphisms in *ORAI1* have been described. In genetic association studies (136 patients with nephrolithiasis and 500 controls), the C allele carrier of rs12313273 in *ORAI1* gene was strongly associated to recurrent stone forming in calcium nephrolithiasis patients [14]. Studies from patients with Ankylosing Spondylitis (AS) indicated a close correlation between haplotypes of *ORAI1* (rs12313273 and rs7135617) and the risk of HLA-B27 positive AS [15]. In addition, a large scale of human DNA screening (2,478 DNA samples from Taiwanese and Japanese populations) also suggests the involvement of *ORAI1* polymorphisms in the susceptibility of atopic dermatitis [16]. These genetics results, combined with the findings in animal studies as well as cellular studies, suggest *ORAI1* might be an important target in immune/inflammatory responses.

In conclusion, the field of store-operated channel has remarkably advanced in the past ten years. With high-throughput genomic screening, we can expect that more exciting findings will be revealed in the near future.

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