Chapter 14

CYLD Cutaneous Syndrome: Familial Cylindromatosis, Brooke-Spiegler Syndrome and Multiple Familial Trichoepitherioma

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1. Introduction

The concept of *CYLD* cutaneous syndrome was proposed by Rajan *et al*. in 2009 (Rajan *et al*., 2009). The syndrome represents an uncommon autosomal dominant disease caused by a germline mutation in the cylindromatosis gene (*CYLD*) (Biggs PJ, *et al*. 1995). *CYLD* cutaneous syndrome is characterized by the development of multiple neoplasms originating from the skin appendages (Rajan *et al*., 2009). It includes three appendageal tumor predisposition syndromes; familial cylindromatosis (FC, MIM 132700), Brooke-Spiegler syndrome (BSS, MIM 605041), and multiple familial trichoepithelioma (MFT, MIM 601606) (Rajan *et al*., 2009). BSS is characterized by multiple skin appendage tumors such as cylindroma, trichoepithelioma, and spiradenoma. FC is typified by multiple cylindromas and MFT by multiple trichoepitheliomas. Here, we summarize current clinical and genetic recognition in *CYLD* cutaneous syndrome.

2. *CYLD* cutaneous syndrome

A genome search using two FC families identified strong evidence for linkage to the locus on chromosome 16q12-q13 (Biggs *et al*., 1995). Subsequently, germline mutations in the tumor suppressor *CYLD* gene were identified in individuals having FC (Bignell *et al*. 2000). A combination of genetic linkage analysis and loss of heterozygosity in 15 FC families showed only the linkage to the locus, providing no evidence for genetic heterogeneity (Takahashi *et al*. 2000). The germline mutations were then detected in individuals with BSS (HU *et al*., 2003; Poblete Gutiérrez *et al*., 2002) and MFT (Salhi *et al*., 2004; Zhang *et al*., 2004; Zheng *et al*., 2004). Affected family members with the same germline mutation in *CYLD* showed FC, BSS or MFT phenotypes, indicating the absence of genotype-phenotype

relationship (Fenske *et al*., 2000; Rajan *et al*., 2009; Young *et al*., 2006). The phenotypic diversity from mild type to severe turban tumor is present in the affected family members with *CYLD* cutaneous syndrome (Biggs *et al*., 1995; Oiso *et al*., 2004; Rajan *et al*., 2009; Young *et al*., 2006). Bowen *et al*. suggested that FC, BSS, and MTF represent phenotypic variation of a single entity (Bowen *et al*., 2005). Rajan *et al*. proposed the term, *CYLD* cutaneous syndrome, for unifying three skin appendage-associated disorders (Rajan *et al*., 2009).

3. The function of CYLD

In 2003, CYLD was shown as a deubiquitinating enzyme that negatively regulates nuclear factor-kappa B (NF-κB) activation (Brummelkamp *et al*., 2003; Kovalenko *et al*., 2003; Trompouki *et al*., 2003; Wilkinson, 2003). NF-κB is involved in controlling inflammation, the immune response, and apoptosis (Pasparakis, 2002). Nowadays, many different cellular functions have been ascribed to CYLD such as proliferation and cell cycle, Ca2+ channel signaling, survival and apoptosis, inflammation, T-cell development and activation, antiviral response, and spermatogenesis (Pasparakis, 2002).

CYLD contains three cytoskeleton-associated protein-glycine-rich (CAP-Gly) domains, two proline-rich motifs, a tumor necrosis factor-alpha (TNF-α) receptor-associated factor 2 (TRAF2) binding site, and ubiquitin-specific proteases (USP) domain responsible for its deubiquitinases (DUB) activity (Harhaj et al., 2011; Pasparakis, 2002). The first two CAP-Gly domains mediate binding to microtubules (Gao *et al*., 2008; Wickström *et al*., 2010), and the third CAP-Gly domain regulates NEMO interactions. NEMO (also known as IκB kinase gamma (IKKγ)) is the regulatory subunit of the IκB kinase (IKK) (Yoshida *et al*., 2011). IKK plays crucial role in activating NF-κB in response to various inflammatory stimuli (Zheng *et al*., 2011). TRAF2 regulates activation of the c-Jun N-terminal kinase (JNK)/c-Jun and the inhibitor of IKK/ NF-κB signaling cascades in response to TNF-α stimulation (Zhang *et al*., 2011).

4. Conclusion

CYLD cutaneous syndrome represents familial cylindromatosis, Brooke-Spiegler syndrome, and multiple familial trichoepithelioma. Further studies for elucidating the function of *CYLD* will focus on defining the multifunctional activities including tumor suppression for neoplasms from the skin appendages.

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