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Chapter 14

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

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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 deubiquitinasases (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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