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TITOLO: Early and late B cell developmental impairment in NFKB1 mutated CVID disease.

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TESTO:

Background: Both the classical (NFKB1; p105/p50) and alternative (NFKB2; p100/p52) NF-kB pathways have been largely studied mainly in animal models. Recently, the role of NFKB2 in human B cell development was recently defined in patients carrying monoallelic mutations in NFKB2 leading to CVID-like disease with autoimmunity and defects in late stages of peripheral B cell maturation. Monoallelic mutations in NFKB1 leading to p50 haploinsufficiency were recently described in a limited number of CVID patients; however, data regarding the effect of monoallelic NFKB1 mutations on B cell development are scarce. Methods: We studied two patients carrying monoallelic mutations in NFKB1, one of which novel, and describe novel findings on the effect of these mutations on B cell development both in early (bone marrow) and late (periphery) stages of maturation. Results: Early stages of B cell differentiation appeared impaired, with a partial maturational arrest at the preBI stage, suggesting therefore a direct role for NF-kB1 in the early stages of human B cell development. In the periphery, both patients showed an expansion of the CD21low population. Interestingly, this expansion of CD21lo B cells was not observed in the NFKB2 mutated patient, suggesting therefore an intrinsic role of the classical NF-kB pathway in the biology of CD21lo B cells in CVID. All NFKB1 mutated patients showed a complete absence of CD27+ switched memory B cells. Conclusions: Taken together, our data provide evidence for a novel role for NF-kB1 in human B cell development, both in the bone marrow and the periphery. Furthermore, the CD21lo population appears particularly expanded in the presence of monoallelic NFKB1 but not NFKB2 mutations, suggesting an intrinsic role for the classical NF-kB pathway in the biology of the CD21lo B cell population, opening novel possibilities for better understanding this peculiar B cell subset, both in CVID and autoimmune diseases, such as SLE.

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