Significant association between TNFAIP3 inactivation and biased immunoglobulin heavy chain variable region 4-34 usage in mucosa-associated lymphoid tissue lymphoma

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Both antigenic drive and genetic change play critical roles in the development of mucosa-associated lymphoid tissue (MALT) lymphoma, but neither alone is sufficient for malignant transformation, and lymphoma development critically depends on their cooperation. However, which of these different events concur and how they cooperate in MALT lymphomagenesis is totally unknown. To explore this, we investigated somatic mutations of 17 genes and immunoglobulin heavy chain variable region (IGHV) usage in 179 MALT lymphomas from various sites. We showed that: (1) there was a significant association between the biased usage of IGHV4-34 (binds to the carbohydrate I/i antigens) and inactivating mutation of TNFAIP3 [encoding a global negative regulator of the canonical nuclear factor-κB (NF-κB) pathway] in ocular adnexal MALT lymphoma; (2) IGHV1-69 was significantly overrepresented (54%) in MALT lymphoma of the salivary gland, but was not associated with mutation in any of the 17 genes investigated; and (3) MALT lymphoma lacked mutations that are frequently seen in other B-cell lymphomas characterized by constitutive NF-κB activities, including mutations in CD79B, CARD11, MYD88, TNFRSF11A, and TRAF3. Our findings show, for the first time, a significant association between biased usage of autoreactive IGHV and somatic mutation of NF-κB regulators in MALT lymphoma, arguing for their cooperation in sustaining chronic B-cell receptor signalling and driving oncogenesis in lymphoma development. Copyright © 2017 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.

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