Abstract #3 | Poster

Linear ubiquitin is critical for transformation and immune evasion of diffuse largeB-cell lymphoma

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Chronic NF-κB signalling driven by activating mutations in the B-cell receptor (BCR) and MyD88 pathways is a hallmark of activated B-cell-like diffuse large B-cell lymphoma (ABC-DLBCL), sustaining malignant proliferation and migration, significantly contributing to poor prognosis and clinical outcome. The linear ubiquitin (linUb) chain assembly complex (LUBAC), composed of HOIP, HOIL-1 and SHARPIN, is a critical regulator of signal transduction downstream of various immune receptors, including the BCR, modulating both, pro-survival and cell-death-inducing signalling via its unique ability to form linUb chains. In the context of oncogenic BCR signalling, LUBAC is recruited to the CARD11–BCL10–MALT1 (CBM) complex, potentiating NF-κB activation and contributing to survival of DLBCL cells. Yet, the role of LUBAC and its linUb-generating activity in the process of lymphoma establishment, development and dissemination remains unresolved. We show that LUBAC-generated linUb is essential for B-cell lymphomagenesis *in vivo*. Importantly, linUb is not merely modulatory but required for BCR-induced NF-κB activation, even in the presence of potent oncogenic drivers which, consequently, are insufficient for malignant transformation when LUBAC is inactivated. Our findings position linear ubiquitination as both necessary and sufficient in distinct contexts: necessary within malignant B cells to sustain NF-κB–dependent transformation, and sufficient within the lymphoma immune micro-environment to establish a supportive signalling network that enables lymphomagenesis. By defining linUb as crucial for tumour-intrinsic and micro-environmental NF-κB signalling, our study establishes LUBAC activity as a core mechanistic requirement for lymphomagenesis and therapeutically tractable vulnerability of DLBCL.