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Generation of Faithful Autochthonous Mouse Models of Mantle Cell Lymphoma

N. A. Mönig[1, 2], C. M. Gräf[1, 2], P. J. Bröckelmann[1, 2], C. Bruzeau[1], Y. Taskiran[1], M. Reese[1, 2], A. Becker[1, 2], G. Knittel[4], H. C. Reinhardt[4], M. Thelen[1, 2], R. D. Jachimowicz[1, 2]

[1] *Max Planck Institute for Biology of Ageing, Mechanisms of DNA Repair, Cologne, North Rhine-Westphalia, Germany*
[2] *University of Cologne, Department I of Internal Medicine, Cologne, North Rhine-Westphalia, Germany*
[3] *University Duisburg-Essen, Department of Hematology and Stem Cell Transplantation, Essen, North Rhine-Westphalia, Germany*

Mantle cell lymphoma (MCL) is characterized by the nearly ubiquitous translocation t(11;14) leading to Cyclin D1 overexpression and frequently harbors additional alterations, including SOX11 overexpression (~90%) and aberrations in *ATM* (42-56%) and *TP53* (16-31%). Despite recent advances, MCL remains incurable with most patients relapsing, highlighting an urgent need for improved biological understanding and novel therapeutics. Progress has been limited by a lack of immunocompetent transgenic mouse models faithfully recapitulating human MCL. Here, we report that B-cell-specific Cyclin D1 overexpression is sufficient to induce MCL-like lymphomagenesis *in vivo* with high penetrance, reduced survival, and systemic disease involving lymphoid and non-lymphoid organs. Tumors frequently displayed disrupted splenic architecture, high proliferative activity and an immunophenotype consistent with human MCL ($CD19^{+}$ $CD23^{-}$ $CD5^{+/-}$ $Bcl6^{-}$ $CD138^{-}$). Molecular analysis revealed oligo- to monoclonal disease lacking somatic hypermutation and class-switch recombination, indicating a germinal center-inexperienced origin similar to human MCL. Importantly, tumors acquired additional genetic alterations commonly observed in human MCL, supporting the biological relevance of the model. Addition of Sox11 overexpression or loss of Atm and/or Trp53 accelerated lymphoma development and reduced survival while reshaping transcriptional and molecular programs paralleling human MCL with corresponding alterations. Taken together, we demonstrate that Cyclin D1 overexpression in B-cells drives MCL-like disease *in vivo* and cooperates with MCL hallmark alterations to enhance aggressiveness. Thereby, these novel immunocompetent *in vivo* models provide unique platforms to dissect MCL pathogenesis, investigate genetic cooperations in disease progression, and test therapeutic strategies in a system that recapitulates a functional tumor microenvironment and genetic complexity of human MCL.