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The delicate balance between DNA damage and repair in B cells

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Outline of this thesis

In this thesis we aim to get a deeper understanding of the role of DNA damage response (DDR) and DNA repair mechanisms in B-cell development, and how these contribute to the prevention of B-cell transformation.

In **Chapter 1**, we reviewed the current literature on the regulation of two mutagenic enzymes that shape B-cell development; recombination-activating gene 1 & 2 (RAG1/2) complex and activation-induced cytidine deaminase (AID). More specifically, we discuss how these enzymes are regulated by the DDR.

The RAG1/2 complex is of crucial importance for lymphocyte development by initiating the rearrangement of both the T-cell receptor (TCR) and B cell receptor (BCR) genes. For these rearrangements to occur, RAG1/2 induces DNA cleavage. Off-target activity of RAG1/2 is involved in the generation of chromosomal aberrations that characterizes several types of B-cell lymphoma and leukemia. Therefore, the proper regulation of its expression and activity is essential to prevent genomic instability. In **Chapter 2** we investigated the regulation of RAG1/2 in normal and transformed precursor-B cells. Mouse Abl transformed pre-B cells and human pre-B-cell acute lymphoblastic leukemia (B-ALL) cells were used as model systems. The role of the nuclear factor kappa-B (NFKB) and phosphoinositol-3 kinase (PI3K)/AKT signaling pathways in the regulation of RAG1/2 expression and activity was studied in this chapter.

The DDR plays an important role in maintaining genomic integrity. In **Chapter 3**, we studied the contribution of this protective response in controling RAG1/2 expression and activity in cells that sustain RAG1/2-dependent and -independent DNA damage. The involvement of the ataxia telangiectasia mutated (ATM) kinase, as one of the main sensor of DNA damage, and its crosstalk with the forkhead box O1 (FOXO1) transcription factor in the regulation of RAG1/2 expression was evaluated in this chapter.

Upon activation, B cells may undergo additional antigen-dependent Ig gene diversifications in secondary lymphoid organs. In the germinal center (GC), B cells undergo somatic hypermutation (SHM) and class switch recombination (CSR). During SHM, single nucleotide substitutions in the antigen-binding coding part of the Ig gene are introduced, which alter the affinity of the antibody. Affinity maturation takes place by selection of B-cell clones that have acquired increased affinity for the antigen. By CSR, the isotype of the expressed Ig is altered, which shapes the effector function of the humoral immune response. Both SHM and CSR crucially depend on AID, which is responsible for

the introduction of mutations in the IgV genes during SHM and DNA double stranded breaks in the Ig switch regions (DSBs) during CSR. Several DNA repair pathways are involved in the resolution of AID-instigated DNA lesions, which in part determine the fate of these lesions. In **Chapter 4** we studied the complex interplay between the base excision repair (BER) and the mismatch repair (MMR) pathways during AID-dependent mutagenesis.

Targeting the DDR has become a bona fide therapeutic strategy for the treatment of a wide range of cancers. In **Chapter 5** we investigated the effects of the NEDD8-activating enzyme (NAE) inhibitor pevonedistat (MLN4924) on human BCR-ABL+ leukemia cells, focused on understanding the mechanism behind its anti-leukemic activity.

In **Chapter 6**, we described the in situ proximity ligation assay (PLA) as a useful novel technique that allows the direct visualization of protein-protein interactions in suspension cells. We used this approach to study DDR-related protein complexes that are formed upon the induction of DNA damage.

In **Chapter 7**, we discuss our findings.