Chromatin remodelers in the DNA double strand break response

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"And hast thou slain the Jabberwock?
Come to my arms, my beamish boy!
O frabjous day! Callooh! Callay!"
He chortled in his joy.

Lewis Carroll, Through the Looking-Glass

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AIM AND OUTLINE

The cells in our body are constantly exposed to DNA damaging agents, either by metabolic processes in the cell or by environmental factors. DNA damage that interferes with transcription and replication may lead to cell death or mutations and ultimately to human disease such as cancer. To safeguard our genome from these every day threats, the cell has evolved an intricate network of defense systems called the DNA damage response which very efficiently counteracts the hazardous consequences of DNA damage. Human syndromes such as ataxia telangiectasia, xeroderma pigmentosum, Nijmegen breakage syndrome, Fanconi anemia as well as multiple types of hereditary cancer (e.g. BRCA1, BRCA2) underlie mutations in important DNA damage response genes, illustrating the connection between genome surveillance and disease. DNA double strand breaks (DSB) are among the most deleterious types of damage and need to be carefully repaired. DSBs are repaired by two main pathways: either by error prone non-homologous end-joining or by high fidelity homologous recombination, which repairs DSBs by using an undamaged homologous DNA strand as a template.

The folding of DNA into chromatin poses a physical barrier for repair proteins to access the damage. In general, chromatin can be relaxed by post translational modification of histone tails and by chromatin remodeling in order to provide access to the DNA. However, it is poorly understood how chromatin remodelers function within the mammalian DNA damage response. Furthermore, although many key players in DSB repair have been identified for some time, their function has not -or only partly- been unraveled.

The aim of the study described was to identify novel factors in the DSB response and to provide further insight in the functional role of novel and established DSB response factors, thereby focusing on chromatin remodelers. First, we searched for novel players in the DSB response and identified three chromatin remodelers. Second, we provide insight in how these different chromatin remodelers function in the DSB response. Third, we underscore the importance of known DSB repair factors in the DNA damage response.

In chapter one, I provide a comprehensive analysis of the literature regarding the role of histone modifiers and chromatin remodelers in the DSB response. In chapters two, three and four, I describe the identification and characterization of three chromatin remodelers, CHD4, SMARCA5 and CHD2, as novel players in the DSB response. Chapter five describes the importance of the RAD51C gene in DSB repair by homologous recombination, maintenance of genome stability and mouse development.

The last section presents a perspective on the research described in this thesis, on the general role of histone modifications and chromatin remodeling in the DSB response and disease progression and on experimental follow up to further unravel the distinct functions of chromatin remodelers during the DSB response.