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Da steh ich nun, ich armer Tor,
Und bin so klug als wie zuvor!

Johann Wolfgang von Goethe (1808)

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OUTLINE OF THIS THESIS

Chapter 1 contains a general overview of the post-translation modification SUMOylation. The enzymes and proteins involved in SUMOylation and biological processes regulated by SUMO are introduced with a focus on SUMO chain formation, SUMO specific proteases and the role of SUMOylation during nucleotide excision repair.

In **Chapter 2** we review literature about how SUMOylation is involved in and regulates proteostasis with or without cross-talk with ubiquitin. Neurodegenerative diseases are often characterized by an unbalanced proteostasis and accumulation of disease associated proteins. Here we discuss how SUMOylation can influence aggregation or solubility of these disease-associated proteins. Also, we review studies that highlight the neuroprotective role of SUMOylation during oxygen and nutrient deprivation as consequence of ischemia.

In **Chapter 3** we aim to identify how SUMOylation is linked to proteostasis. We observe that SUMOylation dynamics upon heat-shock are altered when the proteostatic transcriptional regulator HSF1 is inhibited. We identify that most SUMOylated proteins are targeted for ubiquitin-mediated degradation upon heat shock and that molecular chaperones, transcribed by HSF1, specifically facilitate the degradation of co-modified proteins. We propose that SUMO quickly solubilizes denatured proteins to prevent formation of toxic aggregates and enables chaperone-facilitated degradation.

In **Chapter 4** we use mass spectrometry to identify SUMOylated proteins that are regulated by the SUMO chain editing protease SENP6. We show that multiple groups or proteins are simultaneously regulated including the majority of members of the constitutive centromere-associated network (CCAN). We show that multiple CCAN proteins fail to localize to the centromere upon SENP6 knockdown. We exclude the possibility of SUMO chain-induced RNF4-dependent ubiquitination and degradation and suggest a model in which SUMO chains could interfere with the assembly of the complex at the centromere.

In **Chapter 5** we identify proteins that are regulated by SUMOylation upon ionizing radiation (IR) and ultraviolet (UV) irradiation. The most dynamically SUMOylated protein upon UV irradiation is Cockayne syndrome B (CSB), a protein highly important for the repair of UV induced DNA damage within actively transcribed genomic regions. Those lesions are repaired by transcription coupled nucleotide excision repair (TC-NER) and CSB is one of the first proteins that is recruited to the site of the damage. We identify that the SUMOylation of CSB enhances the recruitment and stabilization of CSB at the damage site as well as the overall efficiency of TC-NER. Furthermore, we show that Cockayne Syndrome A (CSA) regulates the stability of SUMOylated CSB and the ubiquitination of RNA polymerase II (RNApolII).

In **Chapter 6**, I discuss the scientific findings described in this thesis in light of the published literature. Furthermore, this chapter deliberates on new concepts and future perspectives in the field of SUMOylation.