GROUP NAEGELI

Prof. Dr. Hanspeter Naegeli

University of Zurich
Institute of Veterinary Pharmacology and Toxicology
Winterthurerstrasse 260
8057 Zürich

naegelih@vetpharm.uzh.ch
www.ivpt.uzh.ch

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SUMMARY & MISSION STATEMENT

Our research is dedicated to the study of signaling, protein modification and chromatin remodeling pathways that promote genome stability. We are currently focusing on the mechanisms by which histone methyltransferases and chromatin remodelers regulate nucleotide excision repair activity in human cells.

OVERVIEW

Our aim is to understand how the histone methylome allows for DNA damage recognition by the nucleotide excision repair (NER) "big enzyme" machine in human cells. Maintenance of genome stability is essential to prevent cancer and premature aging. The NER machine safeguards the DNA double helix by removing bulky base adducts induced by ultraviolet (UV) radiation, chemical carcinogens, metabolic byproducts and oxygen radicals. The most prevalent bulky lesion arises from the UV spectrum of sunlight or artificial devices, which can induce hundreds of thousands of DNA photoproducts in each skin cell. To be effective, the NER machine must cope with the inherent compaction of its chromatin substrate where DNA is wrapped around histones giving rise to nucleosome arrays. Work in our laboratory demonstrated a novel role of the histone methyltransferase ASH1L in guiding the NER machine to packed chromatin. We are now using protein depletions and gene deletions as well as chromatin immunoprecipitations followed by proteomics analyses to determine the role of (i) methyltransferases that add chromatin-relaxing methyl groups to histones (for example to H3Lys4), (ii) methyltransferases that add chromatin-condensing methyl groups to histones (for example to H3Lys9) and (iii) chromatin remodelers recruited or activated by histone methylation.

SELECTED CANCER RELATED PUBLICATIONS

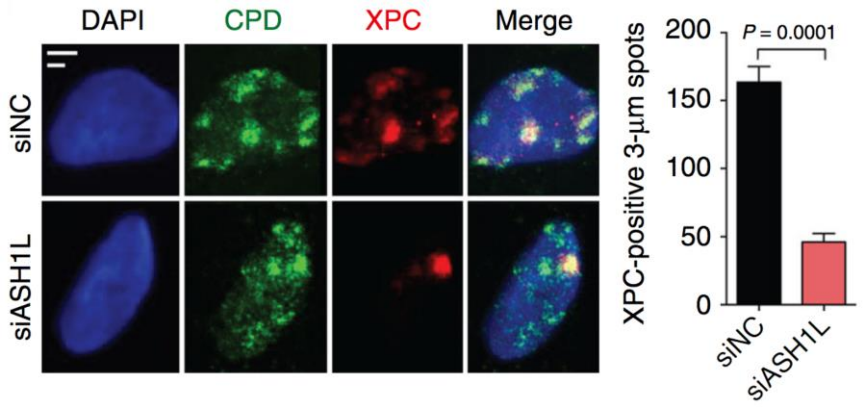
DNA quality control by a lesion sensor pocket of the xeroderma pigmentosum group D helicase subunit of TFIIH. Mathieu, N., Kaczmarek, N., Rüthemann, P., and Naegeli, H. **Curr. Biol.** 2013;23, 204-212.

Chromatin retention of DNA damage sensors DDB2 and XPC through loss of p97 segregase causes genotoxicity. Puumalainen, M.-R., Lessel, D., Rüthemann, P., Bachmann, K., Ramadan, K., and Naegeli, H. **Nat. Commun**. 2014;5, 3695.

Poly(ADP-ribose) polymerase 1 escorts XPC to UV-induced DNA lesions during nucleotide excision repair. Robu, M., Shah, R., Purohit, N., Zhou, P., Naegeli, H., and Shah, G. **Proc. Natl. Acad. Sci. USA** 2017;114, E6847-E6856.

ASH1L histone methyltransferase regulates the handoff between damage recognition factors in global-genome nucleotide excision repair. Balbo Pogliano, C., Gatti, M., Rüthemann, P., Garajova, Z., Penengo, L., and Naegeli, H. **Nat. Commun.** 2017;8, 1333.

Chromatin remodeler CHD1 promotes XPC-to-TFIIH handover of nucleosomal UV lesions in nucleotide excision repair. Rüthemann, P., Balbo Pogliano, C., Codilupi, T., Garajova, Z., and Naegeli, H. **EMBO J.** 2017;36, 3372-3386.



Immunofluorescence image of U2OS cells showing that ASH1L depletion compromises the ability of XPC protein (the NER initiator) to associate with cyclobutane pyrimidine dimer (CPD) lesions. Transfections with siRNA occurred 48 h before UV radiation through 3-µm filter pores (NC, non-coding control). Immunofluorescence was assessed 15 min after a second UV treatment through 5-µm filter pores. Scale bars = 3 and 5 µm. At the time of analysis, the 3-µm spots contain only CPD lesions whereas the 5-µm spots contain a mixture of all UV lesions. Quantifications show the amount of cells displaying XPC protein in the small UV radiation spots tightly bound to CPD lesions (n = 4 with 200 cells in each experiment).