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2023 Winner of the Eppendorf Award for Young European Investigators

»It is an immense honour and I feel humbled to be awarded with the 2023 Eppendorf Award. This would not have been possible without the contribution and spirit of many scientists, be it colleagues or collaborators, as well as mentors and an incredible family I call mine. The award recognises the potential of manipulating enzymatic functions in living cells at will. Using small molecule organocatalysts, we installed new biochemical reactions within an enzyme and have thus succeeded in rewriting the base excision repair pathway. Our research now focuses on a broadening of this technology base by investigating other enzymes and understand biochemical reaction pathways and their biological consequences. Rerouting or reducing oxidative DNA damage depending on individual needs could serve as a new strategy for the development of the precision therapeutics of the future.«

Dr. Maurice Michel

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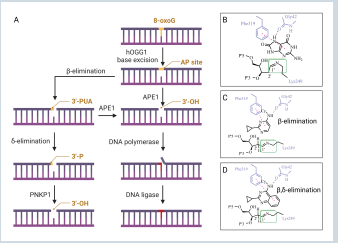
Award-Winning Research

Artificial functions of DNA repair enzymes for the treatment of Disease

Oxidative DNA damage is required for cell homeostasis but may be elevated in human disease, among them inflammation, cancer, neurodegenerative diseases and others. To maintain DNA damage during cell cycles, DNA repair pathways with a significant number of enzymes have evolved in evolution. Due to the low redox potential of Guanine, 8-oxo Guanine (8-oxoG) is the most common product of oxidation in DNA. Within base excision repair, 8-oxo Guanine DNA glycosylase 1 (OGG1) removes 8-oxoG from DNA and forms a Schiff-Base intermediate with the remaining abasic site. OGG1 may cleave the Schiff-Base with the help of the excised free 8-oxoG, termed β-elimination, but not at significant rates in cells. Thus, oxidative conditions within the cell will lead to substantial amounts of OGG1 being bound in the Schiff-Base state. Few proteins exist, that can stimulate OGG1 to cleave the reversible bond to DNA. It is therefore not surprising, that cells appear to use the prolonged residence time of OGG1 on DNA to signal for the binding of transcription factors and the release of inflammatory markers.



DNA lesions may be processed along different routes within base excision repair (A). 8-oxoG excision is dependent on a pathway involving APE1 and cleavage of the intermediate Schiff-Base (green Box, B) is the rate determining step. Organocatalysts of OGG1 stimulate the rate of cleavage of the intermediate, generating structurally distinct repair products (C and D). Thus, depending on the molecule used, base excision repair becomes independent of APE1 or increases DNA damage repair along the evolutionary established route.

Since the discovery of DNA glycosylases DNA repair has experienced significant advancements and the mechanisms of partaking enzymes have been elucidated. In addition, within the last two decades, organocatalysts have emerged as a powerful technology to mimic enzymatic functions using only small organic molecules - among them Schiff-Base chemistry. Traditionally, a union of enzymatic and organocatalytic function has been considered unattractive, since participating in enzymatic functions requires the small molecule to bind close to or in the substrate site, effectively generating a classic inhibitor. Recently, we were first to demonstrate, that this limitation can be overcome for the Schiff-Base complex of OGG1 and DNA. Compared to 8-oxoG, the generated small molecules maintain identical but tighter interactions with OGG1. This binding to the active site of the enzyme increases the Schiff-Base cleavage in cells. Other than 8-oxoG, the synthesized compounds are successful in controlling OGG1 cleavage from DNA through a fine-tuned nitrogen base within their molecular structures. Several series of molecules were developed and enable to rationally chose between an increased, rudimentary but canonical, β-elimination or an artificially generated β,δ-elimination in OGG1. This mode of action equals a molecular switch and changes how cells will have to deal with the arising DNA repair products. This concept opens exciting opportunities in diseases characterized by oxidative DNA damage, for the worse or for the better.

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Read more about our Award winner Dr. Maurice Michel

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