Exploiting synthetic DNA lesions to pinpoint the critical repair pathways

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DNA damage is a well-recognised causal factor of gene dysfunction in cancers and age-related diseases. Because DNA of all living cells is constantly exposed to a variety of reactive endogenous metabolites and environmental toxicants, DNA damage can never be fully avoided and its complexity comprises dozens of structurally different DNA modifications ("DNA lesions"). Knowledge of the lesion-specific responses of cells is required to characterise hazards of exposure to specific genotoxic agents and, from the translational perspective, to identify molecular susceptibility markers and potential targets for personalised therapeutic interventions.

My team exploits synthetic nucleotide derivatives to understand harmful consequences of individual DNA lesions and the lesion-specific repair mechanisms. To model damage induced by food carcinogens, drugs, environmental toxicants and endogenous cellular mechanisms at specific nucleotide positions, we incorporate synthetic analogs of the respective DNA modifications as building blocks into functional reporter genes [1-2]. Delivered to human host cells, such gene constructs can be efficiently used to monitor functional consequences of defined DNA lesions (tolerance versus toxicity), to characterise determinants of damage recognition by individual repair pathways, and to identify redundancy and potential switch points between the pathways [3-7]. I will discuss some recent applications of vectors containing the elements of synthetic nucleic acids to address questions in the fields of DNA repair and epigenetics.

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