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Evaluation of carcinogen exposure via genome-wide DNA-adduct signatures

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Scientific Abstract:

Multiple organs in the body are constantly exposed to a plethora of exogenous carcinogens (e.g., alcohol, tobacco), many of which form DNA adducts, which in absence of repair, can lead to somatic mutations and become the primary cause of cancer. DNA adducts can be used as biomarker of exposure for more personalized screening and prevention strategies, but in reality, only the most common DNA-adducts have been characterized at the molecular level and given the high reactivity of carcinogens, the vast majority of the DNA-adducts are unknown and their mutagenic potential not established. Traditional assays can precisely discriminate adducts on a chemical basis but are not easily scalable to clinical samples with unknown, diverse exposures and cannot provide information about interactions with the functional genome (repair, transcription, replication). In this project, we propose to validate and apply a novel genome-wide assay (Ad-Seq) to globally examine the landscape of DNA damages, agnostic to the chemistry of the adduct, and will utilize the resulting profiles to predict exposure and compare damages in the DNA of various tissue types to mutational signatures identified in the adjacent tumor DNA. This work will establish Ad-Seq profiles and its derived signatures as a novel type of biomarker for cancer prevention, reporting on the global molecular consequences of carcinogens on the DNA and providing a more direct and richer context to investigate DNA-adducts associations with mutagenic exposure and potential mutagenicity.

Lay Abstract:

Multiple organs of the body are constantly exposed to a plethora of carcinogens from exogenous origin (e.g., alcohol, tobacco, pollution), or due to endogenous processes (inflammation, infection), many of which reacts with the DNA. These damages, called DNA adducts, in absence of repair, can lead to somatic mutations and become the primary cause of cancer. Importantly, and similar to what has been observed for tumor mutations, every tissue in every patient likely has a unique set of damages representing a signature of their life-long exposures and subsequent modeling by cellular processes and inherited genetics. In this project, we will validate and apply a novel genome- wide assay (Ad-Seq) to globally examine the landscape of DNA adducts, ignoring their exact chemistry but rather relying on their genomic location and DNA sequence preference. We will utilize the resulting molecular profiles to predict exposure and compare damages in the DNA of normal tissues to mutations found in the adjacent tumor. This work will establish Ad-Seq profiling as a novel tool to assess personal cancer risk, integrating both environment and genetics, reporting on the global molecular consequences of carcinogens on the DNA. The approach will therefore provide a more direct and richer context to investigate the link between mutagenic exposure and subsequent mutations, leading to more personal prevention and screening strategies.