Unraveling the Achilles' Heel of Human Tumors: Moving Towards Inducing Mutational Meltdown by Deciphering the Most Deleterious Mutational Processes

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Although previous research has studied the subfields of cancer genomics and population genetics separately, they have rarely merged. This study combines the knowledge of mutational signatures (used within oncology research), distribution of fitness effects, DFE (used within population genetics), and EXchangeability (EX) scores (used within biochemistry). This novel crossover between statistics and biochemistry into cancer research allows potential therapeutic strategies to be introduced to induce the most harmful mutational processes in tumor cells to ultimately achieve a mutational meltdown of the tumor population. This research investigates the mean deleterious effect of known somatic mutational processes in humans. For the first time, the DFE of each mutational process found in human tumors is constructed. The project was conducted by downloading data from the 1000 Genomes Project and splitting the polymorphism data by their 3mer mutation class. The diffusion method dadi was used to infer the distribution of fitness effects of new non-synonymous 3mer mutation types in a large sample of 100 Yoruba individuals. SBS90 and SBS22 were found to be the most deleterious somatic mutational signatures. We validated DFE inferences using an orthogonal measure based on deep mutational scanning. Close examination of the mutational spectra for both signatures revealed predominantly T>A mutations. This study has implications towards inducing mutational meltdown in specific tumor populations.

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