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Modelling mutational signatures of environmental carcinogens in cultured human cells

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Abstract

Whole genome sequencing (WGS) of human tumours has revealed distinct patterns of mutation that hint at the causative origins of cancer. The Catalogue of Somatic Mutations in Cancer (COSMIC) is a global resource for information on somatic mutations in human cancer and currently lists 30 distinct mutational signatures. Some signatures are correlated with known environmental exposures, but the causative origins of many signatures remain unknown. We have developed an experimental approach using human induced pluripotent stem (iPS) cells to define mutational signatures of environmental carcinogens by WGS. Treatment conditions (e.g. concentration) for WGS were optimized by assessing cytotoxicity, DNA damage response signaling and the formation of premutagenic DNA adducts. After WGS, a ubiquitous background mutational signature was extracted in all clones showing similarities with COSMIC Signature 18 which has been reported in other cultured human cells. Specific signatures were identified in human iPS cells, following exposure to benzo[a]pyrene (BaP), simulated sunlight aristolochic acid I (AAI) and aflatoxin B1 (AFB1), revealing characteristic mutation pattern for each carcinogen that were highly similar to COSMIC signatures of mutations found in tumors of individuals who were exposed to the agent of interest: predominantly G to T mutations for BaP were linked to COSMIC Signature 4; C to T for simulated sunlight was linked to COSMIC Signature 7; A to T for AAI was linked to COSMIC Signature 22; and G to T for AFB1 was linked to COSMIC Signature 24. Thus, human cell-based systems and WGS can be used to study the genome as a record of environmental exposure. Recent Publications 1. Long A S, Wills J W, Krolak D, Guo M, Dertinger S D, et al. (2018) Benchmark dose analyses of multiple genetic toxicity endpoints permit robust, cross-tissue comparisons of MutaMouse responses to orally delivered benzo[a]pyrene. Arch. Toxicol. 92(2):967???982. 2. White P A, Douglas G R, Phillips D H and Arlt V M (2017) Quantitative relationships between lacZ mutant frequency and DNA adduct frequency in Muta???Mouse tissues and cultured cells exposed to 3-nitrobenzanthrone. Mutagenesis 32(2):299??? 312. 3. Kucab J E, Zwart E P, van Steeg H, Luijten M, Schmeiser H H, et al. (2016) TP53 and lacZ mutagenesis induced by 3-nitrobenzanthrone in Xpa-deficient human TP53 knock-in mouse embryo fibroblasts. DNA Repair 39:21???33. 4. Nik-Zainal S, Kucab J E, Morganella S, Glodzik D, Alexandrov L B, et al. (2015) The genome as a record of environmental exposure. Mutagenesis 30(6):763???70. 5. Kucab J E, van Steeg H, Luijten M, Schmeiser H H, White PA, et al. (2015) TP53 mutations induced by BPDE in Xpa-WT and Xpa-Null human TP53 knock-in (Hupki) mouse embryo fibroblasts. Mutat. Res. 773:48???62. There are many ways by which to define "environmental" carcinogens. Here the epithet "environmental" is taken to cover any unwanted, environmentally derived chemicals that enter the human body via food, drink or air and that have been shown to cause, or are suspected of causing, cancer in humans and/or experimental animals. As a further qualification, only man-made materials will be considered, with the exception of radon. The definition includes environmental contaminants in' food but excludes food additives and natural ingredients. Mytotoxins, passive smoking and occupational carcinogens will not be dealt with because they are discussed elsewhere in this book. Furthermore, the effects of chlorofluorocarbons on stratospheric ozone levels, and thus indirectly on ultraviolet radiation and skin cancer, are beyond the scope of this chapter. Environmental carcinogens are discussed here by chemical group rather than by source of exposure. However, in the context of each chemical the different sources of exposure are presented, and quantitative data will be given when feasible. Before individual chemicals are considered, the fate of chemicals in the environment, classification of carcinogens, variation in the populations exposed and principles of risk estimation will be discussed. Environmental carcinogenesis is a very wide field covering environmental hygiene, human exposure assessment, carcinogenic properties of chemicals and some degree of risk assessment. For this reason several sources have been consulted in preparing this chapter. The World Health Organization has published valuable reference material in this area such as Guidelines for Drinking-Water Quality (WHO 1984a), Air Quality Guidelines (WHO 1987a) and Environmental Health Criteria on a number of compounds; the Environmental Protection Agency of the United States of America (U.S.EPA) has assessed human exposure to and risks from a variety of environmental carcinogens, and many of these risk estimates are quoted here. The Monographs series of the International Agency for Research on Cancer offers authoritative, qualitative assessments on the carcinogenic properties of chemicals and data on the occurrence of these chemicals in the environment; furthermore, the periodicals Environmental Carcinogenesis Reviews and Environmental Health Perspectives are invaluable sources of reference data in the areas to be covered in this chapter. Sampling and analytical techniques in environmental hygiene have developed considerably during the past 2 decades. The accuracy of the methods has improved, and sensitivities have increased by orders of magnitude for some measurements. The older results thus need to be treated with due caution. The greatest problem is, however, the

paucity of measurements. Rarely are representative measurements available, even for one subpopulation that cover all the possible sources of exposure. This being the case, extrapolations even to a national level may be tenuous and extrapolations to a global level are sheer guesswork. There are many ways by which to define "environmental" carcinogens. Here the epithet "environmental" is taken to cover any unwanted, environmentally derived chemicals that enter the human body via food, drink or air and that have been shown to cause, or are suspected of causing, cancer in humans and/or experimental animals. As a further qualification, only manmade materials will be considered, with the exception of radon. The definition includes environmental contaminants in food but excludes food additives and natural ingredients. Mycotoxins, passive smoking and occupational carcinogens will not be dealt with because they are discussed elsewhere in this book.

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