

Translating Mutagenesis into Carcinogenesis

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Editorial

The Journal of Carcinogenesis and Mutagenesis follows a now century-old tradition of publishing investigations into the genetic, i.e., mutational, basis of cancer. Insights from our field have been, and continue to be, critically important for human cancer treatment, detection and prevention.

Genotoxicity provided the rationale for systemic cancer therapy, which is only, now, after 70 years or so, giving way to new modalities. It is becoming standard practice to evaluate the genome and/or transcriptome of cancers in order to tailor targeted therapies using antibodies (and now, fusion antibodies), small molecule inhibitors, and, in the near future, microRNAs, both native and engineered. These methods usually target the altered or over expressed products of activated oncogenes; normal cellular genes activated by site-specific mutation.

Altered cellular proteins activated oncogenes or inactivated (i.e., DNA hypermethylated) tumor suppressor genes can also be found in cellular surveys or bodily fluids, allowing for detection of the cancer prior to overt tumorigenesis, or even at the preneoplastic stage.

It is, however, at the level of prevention where the field of genotoxicity has made its greatest contributions to human health, and where it may play its most important roles in the future. It is impossible to estimate the number of cancer cases prevented by the governmental and industrial screening of chemicals and products for mutagenic activity, which have then not been introduced into wide human contact.

Arguably, however, we have not been as successful at identifying and removing carcinogenic agents already in the environment. The classification of such agents at the highest, actionable, level requires unambiguous human epidemiological data, a level of stringency that is almost impossible to attain. Indeed, it is almost as if a Hiroshima-scale exposure event is required for every individual carcinogenic agent. Real-world exposures are unlikely to provide the power necessary for strong associations with a disease such as cancer, which has long been known to require multiple events.

Rather than focusing on the carcinogen, however, the multi-step model of cancer provides an alternate approach for human carcinogenesis, analysis of humans themselves. The rationale is simple: if multiple events are required to induce cancer, and most, if not all such events are mutations (we must leave room for epigenetic events, mechanisms that mimic genetic events [1]), then cancer should occur differentially in individuals and populations with high frequencies of mutation.

This was the basis of a series of studies applying our oldest mutational assays, cytogenetic analyses of lymphocyte chromosomal aberrations, micronuclei and sister chromatid exchange prospectively to populations in a number of countries around the world [2-6]. It quickly became clear that chromosomal aberration frequency was predictive of subsequent cancer incidence and/or mortality, an observation that has held up over time [7]. Indeed, with the accumulation of studies and follow-up time, micronucleus frequency was also found to be predictive

of cancer [8,9]. Just to show that all cytogenetic analyses are not equally applicable, sister chromatid exchange remains unpredictable.

An important aspect of these studies has been that although the original populations chosen were often targeted due to known or expected exposures, the authors acknowledge the importance of and variability of individual susceptibility in their models [10]. Too often, such studies have been weighted towards either exposure (toxicologists) or predisposition (geneticists) with little allowance for the interaction of such factors. The integration of individual response into exposure measurements was advocated in 1983 by Hsu [11], and we have observed considerable inter-individual variability in measurement of human DNA repair capacity [12].

So, with two successful, predictive measures of cancer risk validated and available, why has there been no effort to apply these techniques in population screening? One reason appears to be the lack of specificity of the results. Since these studies amalgamate populations assayed in different laboratories, the authors felt justified in separating the assay results only in tertiles, with the highest tertile showing a consistent, but relatively modest relative risk of cancer on the order of two-fold. There also seems to be some perceived resistance to the minimally invasive phlebotomy required to obtain samples for these analyses, with current efforts apparently attempting to standardize assay procedures and shift the focus to non-invasively obtainable buccal cells [13]. In a world where single measurements are predictive of cancer and blood samples are available after any doctor visit, this seems like progress sideways rather than forward.

Another approach to measurement of human somatic mutation has been the development of a number of gene-specific assays [14]. Due to the feasibility requirement of detecting mutations with single-hit kinetics in a diploid organism (humans), there have never been many such assays, with early techniques targeting the β -hemoglobin and HLA genes having fallen by the wayside, only to be replaced by methods focusing on the T cell receptor [15] and PIG-A [16,17] loci.

The two most widely applied of these types of methods, the HPRT assay in lymphocytes and the GPA assay in erythrocytes, have also been applied in retrospective studies comparing the mutation frequencies in newly diagnosed cancer patients and controls [18]. In both assays, the patient population exhibited a 1.5-fold increased mutation frequency that was statistically significant.

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The GPA assay was developed as a biodosimeter for ionizing radiation, but has since been validated in a number of exposure scenarios [19]. It has also been found to be diagnostic for certain inherited DNA repair deficiency syndromes [20,21]. If “outliers” are discriminated in the normal and cancer patient populations as defined for diagnostic purposes, they have an odds ratio of over 4 of preferentially occurring among the patients. Although the proportion of such individuals with unusually high GPA mutation frequencies varies significantly with age [22], it averages about 10% of the normal population, a more manageable proportion for targeted analysis, monitoring or treatment.

Several other types of analysis have also been reported to be predictive of cancer in human populations, such as mutagen sensitivity [23] and screening of blood for oncogene mutations [24] and methylated tumor suppressor genes [25]. Perhaps it is time to shift our emphasis from debating the best tests for chemical screening (again) [26,27] to determining the best set of tests to prospectively defining cancer risk in human populations?

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