

INTERDISCIPLINARY RESEARCH: WHERE LABORATORY AND EPIDEMIOLOGY COMBINE AND COMPLEMENT

ONE OF THE KEY FEATURES OF THE AGENCY'S STRATEGY HAS BEEN THE EMPHASIS PLACED ON CONDUCTING RESEARCH THAT INTEGRATES LABORATORY SCIENCES AND POPULATION-BASED STUDIES. THE IMPORTANCE OF INTERDISCIPLINARY RESEARCH TO IARC'S MISSION WAS RECOGNIZED FROM ITS INCEPTION AND THE AGENCY'S PIONEERING APPROACH IN THIS AREA WAS, AND REMAINS, ONE OF THE MAIN CONTRIBUTORS TO ITS SUCCESS.

Increasingly, the expanding knowledge about mechanisms of carcinogenesis in relation to genetic and epigenetic alterations, combined with the development of 'omics' technologies, is opening new possibilities for combining laboratory-based and epidemiological research. These developments present unprecedented opportunities to further the understanding of both the causes and mechanisms of cancer, as well as providing the scientific rationale for its prevention and, thus, for the translation of research findings from the laboratory to the population. Indeed, it is this approach which promises to provide new impetus to epidemiological studies which seek to detect small effect sizes in exposure-disease associations.

Research that cuts across groups and different specialities within the Agency is highlighted here to provide some specific examples where this interdisciplinary approach is yielding valuable insights. These include not only epidemiological studies incorporating biomarkers, but, of equal importance, studies where observations in the population led to subsequent laboratory studies aimed at explaining those observations.

ROLE OF NICOTINIC ACETYLCHOLINE RECEPTORS IN TOBACCO-INDUCED LUNG CANCER

Genome-wide association studies, coordinated by Agency scientists, identified a susceptibility locus in chromosome region 15q25 that is strongly associated with lung cancer. Among the genes in this region were three encoding nicotinic acetylcholine receptor (nAChR) subunits (CHRNA5, CHRNA3 and CHRNB4); one variant of CHRNA5 was among the markers with the strongest disease association (Hung *et al.*, 2008).

nAChRs bind to nicotine and tobacco nitrosamines (such as N'-nitrosonornicotine) as well as to other potential lung carcinogens. Certain nAChR subunit alleles have been shown to be associated with a small but significant increased risk of lung cancer in smokers, but no clear association is observed in non-smokers or with other tobacco-related cancers (pancreas, bladder). Given these epidemiological observations, there is a need to understand the functional consequences of the polymorphisms identified to interpret the significance in relation to cancer prevention.

A research consortium coordinated by IARC scientists (BioSILC) and involving the IARC MOC and EGE Groups, the 'Institut Pasteur' in Paris and INSERM in Reims, demonstrated that the association between nAChR genes, tobacco and lung cancer risk is mediated through a complex interaction of multiple mechanisms: polymorphisms in CHRNA5 predispose to nicotine dependence with some alleles strongly associated with tobacco use (Frahm *et al.*, 2011); CHRNA5 expression in bronchial cells modulates cell adhesion and motility, and regulates the expression of p63, a potential oncogene in squamous cell carcinoma (SCC) (Krais *et al.*, 2011); CHRNA3 gene expression is frequently reduced in lung cancer cells, through DNA hypermethylation, and restoring CHRNA3 expression in these cells induces apoptotic cell death, providing a possible novel mechanism for lung cancer therapy (Paliwal *et al.*, 2010).

ROLE OF β CUTANEOUS HPV TYPES IN SKIN CARCINOGENESIS

Another good example of the complementarity between laboratory sciences and epidemiology at the

Agency is provided by the study of the role of β cutaneous HPV types in skin carcinogenesis, carried out by the IARC ICB Group in collaboration with researchers from the German Cancer Research Centre (DKFZ) (for a more detailed summary of this study see pg. 80 below).

Epidemiological and biological data suggested a role for solar exposure and immune impairment in the etiology of non-melanoma skin cancer (NMSC). Additional evidence pointed to cutaneous β HPV types as the infectious agents possibly responsible for the observed association with immune status, although it remained unclear whether they played a direct role.

In a first series of experiments, the expression of the main oncoproteins of cutaneous β HPV types (HPV38 E6 and E7 proteins) was shown to disrupt several key signalling pathways involved in the control of cellular proliferation and apoptosis (Accardi *et al.* 2011; Hussain *et al.* 2011; Yue *et al.* 2011). These results were confirmed by the observation of increased cellular proliferation in the epidermis of transgenic mice expressing HPV38 oncoproteins in the skin under the control of the keratin 14 promoter. More significantly, chronic UV exposure induced the formation of pre-malignant skin lesions and SCC in a significant proportion of transgenic animals, but not in wild-type animals. Moreover, the pre-malignant skin lesions induced by UV irradiation in the transgenic mice resembled actinic keratosis lesions in humans, which are considered as precursors of SCC (Viarisio *et al.*, 2011).

This work demonstrates that the oncoproteins of β HPV types can promote the development of SCC in mouse skin by enhancing the carcinogenic effect of UV irradiation. These data further support the role of β HPV types in the development of NMSC in humans.

The two studies described above provide particularly good examples of Agency research where data from genomics and/or epidemiological studies led to the development of novel hypotheses and guided the design of functional studies which, in turn, provided significant insights into some of the mechanisms

of carcinogenesis associated with important risk factors for two common human cancers.

USE OF BIOMARKERS IN EPIDEMIOLOGICAL STUDIES

Advances in our understanding of the mechanisms of carcinogenesis have led to the development of new or improved biomarkers of exposure, susceptibility and diagnosis or staging of cancer, which are transforming epidemiological research. However, the use of biomarkers in the context of large epidemiological studies is technically demanding, requiring methods which combine high sensitivity, high-throughput, robustness and limited cost.

The activities of the BMA Group are focused specifically on the development of assays which can be applied to large cohort and case-control studies of cancer. Both immunoassays and chromatographic analyses for the accurate measurement of biomarkers of nutrition (fatty acids and carotenoids), metabolism (sex steroids, growth factors, insulin and obesity-related hormones and thyroid hormones) and inflammation (cytokines) have been established.

The assays mentioned above have been successfully applied to major existing cohorts with biological specimens (the European Prospective Investigation into Cancer and Nutrition (EPIC), the New York University Women's Health Study, The Multiethnic Cohort, the Northern Sweden Health and Disease Study, the DOM cohort and the Study of Hormones and Diet in the Etiology of Breast Cancer-ORDET) to study the etiology of many cancers (breast, endometrial, ovary, prostate, colorectal, cervical and thyroid). A total of about 12 000 analyses on 3500 samples have been carried out over the last biennium, mainly focusing on hormone analyses for studies on cervical and thyroid cancers (in collaboration with the ICE Group) within the EPIC cohort.

Among the main results of these studies is the finding that testosterone, and possibly estradiol, may be implicated in the etiology of invasive cervical carcinoma (Rinaldi *et al.*, submitted) These results suggest that the use of modulators of sex steroid hormones may help to improve

the treatment of invasive cervical cancer by decreasing recurrences of cancerous and precancerous lesions.

RESEARCH LEADERSHIP FORUMS

Finally, a new initiative to promote interdisciplinary research at the Agency was introduced at the end of the biennium. The Research Leadership Forums consist of one day meetings of senior scientific staff at a location in or around Lyon, with the purpose of discussing the Agency's scientific strategy and activities in specific areas of cancer research. The aim of these meetings is to stimulate discussion between IARC Groups and promote the development of research projects that cut across individual areas of research. The first of these meetings took place in December 2011 and focused on the Agency's strategy on breast cancer.

PUBLICATIONS

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