The relationship between dietary exposures and cancer outcomes has been the focus of an immense amount of research over the past few decades. There are numerous challenges facing analytical epidemiologic studies, including issues of confounding, precision of dietary instruments, and complex mixtures. Biomarkers for specific nutrients or broad groups of nutrients have helped to provide a more objective assessment in some cases, and recently there has been interest in the use of gene-nutrient interactions to shed light on the mechanisms and provide support for a biological basis to these relationships.

The gene-nutrient relationship is a bi-directional one: availability of specific compounds regulates gene expression, and conversely, much of the response of the body to these nutrients is genetically determined. Technological approaches to studying these interactions include the use of knockout mice, association studies using candidate-genes, and DNA microarrays.

Investigating associations between nutrient intake and polymorphisms occurring in putative genes in their metabolic pathways is a potential tool for clarifying the carcinogenic process. Examples in the literature include the study of genes, which contribute to endogenous antioxidant capacity, such as superoxide dismutase (MnSOD), and dietary antioxidants in breast cancer risk; as well as the interaction between folate status, and MTHFR gene mutations in determining DNA methylation. Using the 'Mendelian randomization' approach, it is possible to see if individuals stratified on the basis of their metabolic genotype exhibit differences in the effect of dietary components that mirror the effects that would be predicted by the metabolic pathways involved. The influence of glutathione S-transferase on the chemoprotective effect of isothiocyanates from cruciferous vegetables is an application of this approach.

Immunogenetics factors in chronic beryllium disease

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Exposure to beryllium in the workplace can cause beryllium sensitization and chronic beryllium disease. Sensitization to beryllium can be detected in the laboratory using a beryllium lymphocyte proliferation test. It was shown that anti-HLA antibodies could block the beryllium-specific response in the beryllium lymphocyte proliferation test, thereby implicating HLA-genes in chronic beryllium disease. A supratypic genetic marker, *HLA-DPB1*^{E69}, has been shown to be strongly associated with immunologic sensitization to beryllium and chronic beryllium disease in beryllium workers. Among the 36 *HLA-DPB1* gene variants that code for E69, molecular epidemiological studies have suggested a risk hierarchy; where some variants appear to convey low to moderate risk (e.g., *HLA-DPB1*0201*, ~2-fold), some convey an intermediate risk (e.g., *HLA-DPB1*1901*, ~5-fold) and others convey high risk (e.g., *HLA-DPB1*1701*, >10-fold). Computational chemistry has been used to further investigate a potential mechanistic basis for these observations. A strong correlation has been found between the hierarchical order of risk of chronic beryllium disease associated with specific alleles and the predicted surface electrostatic potential of the corresponding isotypes. This approach has further been used to predict the binding affinities of different residues for positively charged beryllium ions in different HLA-DPB1 molecules. These findings suggest that preferential cation binding to specific HLA amino acid sequences in a putatively metal-free antigen-binding pocket might selectively alter the innate specificity of antigen recognition. In addition, it may be possible to use a computational chemistry approach to identify candidate susceptibility genes for further investigation of occupational diseases.

DISEASE MARKERS

ABSTRACTS OF ICT-X SATELLITE MEETING ON MOLECULAR BIOLOGY

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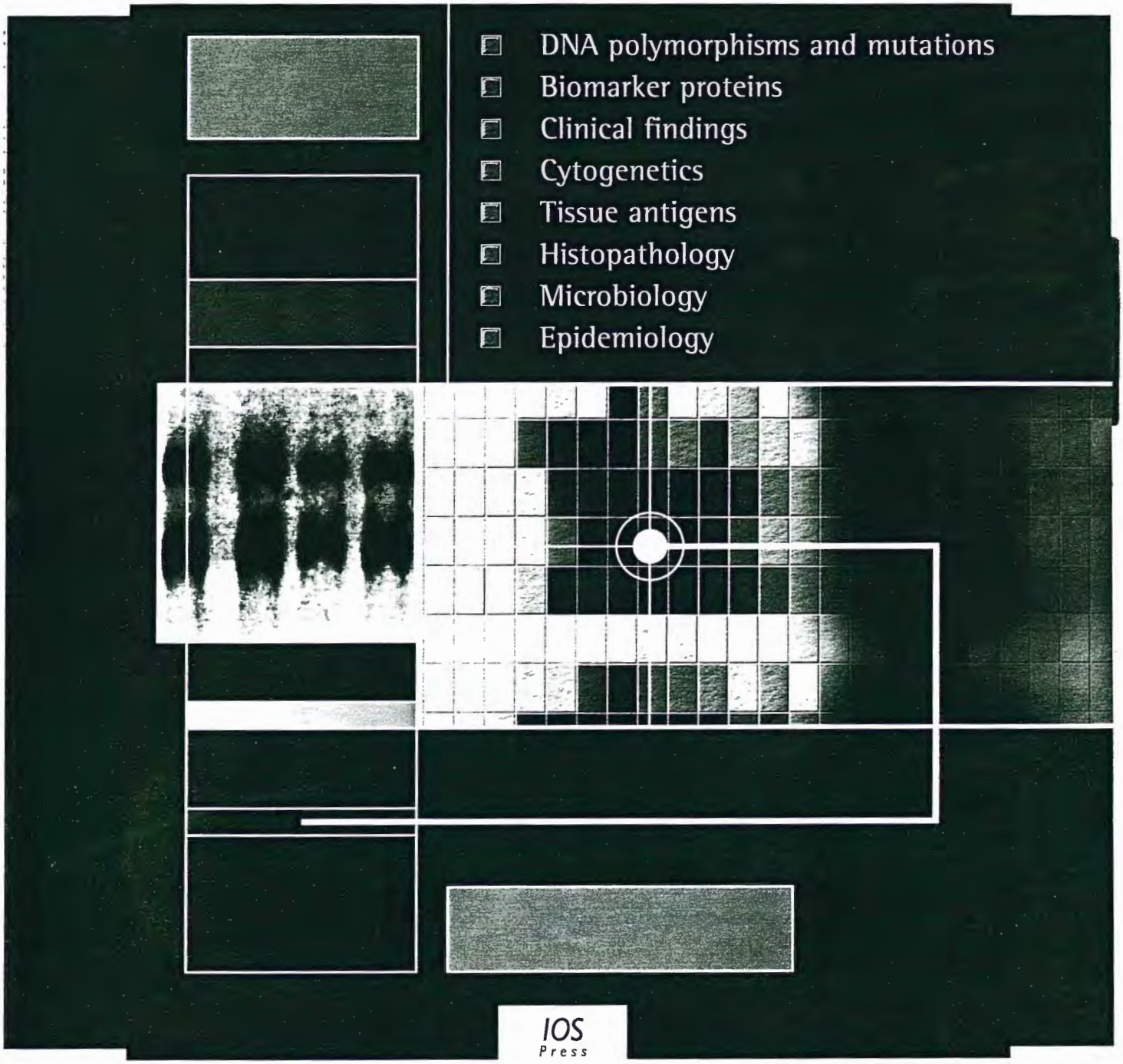

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