Inflammatory Genomics

As a University of London undergraduate beginning a module on pathology, I remember Professor Frank Fairweather opening his lecture by pointing to a large boil on his forehead as an example of acute inflammation. He then proceeded to describe the gross pathological characteristics of acute inflammation: weal, brief blood vessel constriction, followed by blood vessel dilation and associated redness. Such was my introduction to the most common consequence of tissue damage—and contributor to disease pathogenesis—inflammation.

Inflammation is mediated by chemical activators, collectively known as chemokines, secreted in the area of the tissue damage. Chemotactant proteins are expressed on the endothelial cell of the dilated blood vessels that serve as recruitment factors for lymphocytes. Blood vessel dilation causes a decrease in local blood flow, and activated neutrophils, attracted by the chemokines, attach to the chemotactant proteins, squeeze themselves through the endothelial cell walls of the locally dilated blood vessels, and follow the scent of the chemokines to the site of damage (for additional information, see Schmidt 2005).

Toxicogenomics has led to an additional description of inflammation based on the differential expression of genes associated with the inflammatory process. One of the first toxicogenomics reports published was that of the differential expression of genes in response to lipopolysaccharide-induced inflammation (Heller et al. 1997). Several reports now link the expression of certain genes, in particular the attachment genes Icam1 and Icam1, to, for example, inflammation in the liver (Davies et al. 2005; Gant et al. 2003; Huang et al. 2004; Jiang et al. 2004). To date, a quantitative fingerprint of gene expression associated with inflammation has not been defined. In the GeneOntology (GO) database (GO 2005), genes associated with, but not necessarily quantitative for, inflammation are identified in biological processes as “inflammatory response.” Under inflammatory response in the GO, there are 371 genes listed for Homo sapiens. Tumor necrosis factor-α (TNF-α) is included among these 362 genes, but interleukin 6 (IL-6) is not, although IL-6 is used as a plasma biomarker of inflammation (Curran et al. 2005). Similarly, a recent study in the liver has associated three genes PGs6 (pregnancy-specific β-1-glycoprotein), Gstm4/M2 (glutathione S-transferase mu 4 and mu 2), and Oat (ornithine ketoacid aminotransferase) with inflammation in human liver (Younossi et al. 2005); these genes, like IL-6, are not categorized as inflammation genes in the GO. Thus, not all genes associated with inflammation are defined as such in GO, and none are quantitatively associated. Therefore, to provide a repository of data for making future associations, we need a maintained sub-database of differential gene expressions that are quantitatively associated with measured pathological responses. Such quantitative association of gene expression with altered pathology, known as “phenotypic anchoring” (Moggs 2005; Moggs et al. 2004; Paules 2003; Waters and Fostel 2004), includes measurement of both gene expression and degree of pathological change. Few data sets in Gene Expression Omnibus (GEO 2005) or ArrayExpress (European Bioinformatics Institute 2005) contain a histopathological quantitation of inflammation of sufficient quality to allow retrospective phenotypic anchoring of differential gene expression at the present time. More data sets need to include an actual measure of pathological change. In particular, toxicogenomic data should be collected before and during the onset of measured pathological change.

However, before embarking on the development of a phenotypically anchored database of signature gene expression, we must ask the following question: Does toxicogenomics have any advantage over histopathology in the assessment and characterization of pathological change? For inflammation, as for other pathologies, the answer to this question depends on whether toxicogenomics can a) detect inflammation before it becomes histopathologically observable, b) provide a more quantitative assessment of its severity, and c) distinguish between the acute and chronic forms and other pathologies. If we are referring to the most informative genes, the answer to these questions is probably “yes,” but more data is necessary to derive conclusive answers. Thus, the generation of more gene expression data is necessary in targeted pathologies such as inflammation, and a phenotypically anchored database should be targeted to specific common pathologies in the first instance so critical data masses of gene expression data can be collected.

In the early development of microarrays and their application in toxicology, some predictions were made that histopathologists would become an endangered species, made redundant by the new technology. This has not happened, and even the reverse could be argued to have occurred; toxicogenomics has proven so challenging for interpretation that there has been a retreat into the “gold standard” methods of analysis (Albertini 2005). Toxicogenomics has the potential to inform and append histopathological assessment, injecting a degree of instrumental precision into the analysis and assisting in the differentiation of difficult-to-discern lesions (Gant 2002, 2003; Lakhani and Ashworth 2001). Although there is still much work to be done, toxicogenomics will gradually gain a central role in the toxicologists’ armory—as long as expectations are reasonable, quality is good, interpretation is expert, and conclusions are balanced. Genomics has much to offer in pathological assessment, but its application should be collaborative, not inflammatory.

Timothy W. Gant is head of the Systems Toxicology group at the Medical Research Council Toxicology Unit, United Kingdom. The primary interests of the group are the application of genomics in molecular toxicology with emphasis on the genetic basis of susceptibility and resistance to toxicity.

Timothy W. Gant
Medical Research Council Toxicology Unit
University of Leicester
Leicester, United Kingdom
E-mail: twg1@le.ac.uk

The author declares he has no competing financial interests.
REFERENCES

Albertini S. 2005. Toxicogenomics in the pharmaceutical industry: hollow promises or real benefit? Mut Res 575:102–115.

Curran JE, Jowett JB, Elliott KS, Gao Y, Gluschenko K, Wang J, et al. 2005. Genetic variation in selenoprotein S influences inflammatory response. Nat Genet 37:1234–1241.

Davies R, Schuurman A, Barker CR, Clothier B, Chernova T, Higginson FM, et al. 2005. Hepatic gene expression in protoporphyric Fech mice is associated with cholestatic injury but not a marked depletion of the heme regulatory pool. Am J Pathol 166:1041–1053.

European Bioinformatics Institute. 2005. ArrayExpress. Available: http://www.ebi.ac.uk/arrayexpress/ [accessed 7 November 2005].

Gant TW. 2003. Application of toxicogenomics in drug development. Drug News Perspect 16:217–221.

Gant TW, Baus PR, Clothier B, Riley J, Davies R, Judah DJ, et al. 2003. Gene expression profiles associated with inflammation, fibrosis, and cholestasis in mouse liver after Griseofulvin. Environ Health Perspect 111:847–853.

GO. 2005. Gene Expression Omnibus. Available: http://www.ncbi.nlm.nih.gov/geo/ [accessed 7 November 2005].

GO. 2005. GeneOntology, Biological Process. Available: http://www.geneontology.org/ontology/process.ontology [accessed 7 November 2005].

Heller R, Schena M, Chai A, Shalon D, Nemethy G, et al. 1997. Discovery and analysis of inflammatory disease-related genes using cDNA microarrays. Proc Natl Acad Sci USA 94:2150–2155.

Huang Q, Jin X, Gaillard ET, Knight BL, Pack FD, Stoltz JH, et al. 2004. Gene expression profiling reveals multiple toxicity endpoints induced by hepatotoxicants. Mutat Res 549:147–168.

Jiang Y, Kang YJ, Liu J, Waalikes M. 2004. Changes in the gene expression associated with carbon tetrachloride-induced liver fibrosis persist after cessation of dosing in mice. Toxicol Sci 79:404–410.

Lakhani S, Ashworth A. 2001. Microarray and histopathological analysis of tumours: the future and the past? Nat Rev 1:151–157.

Moggs J. 2005. Molecular responses to xenostrogens: mechanistic insights from toxicogenomics. Toxicology 213:177–193.

Moggs J, Tinwell H, Spurway T, Chang HS, Pate I, Lim F, et al. 2004. Phenotypic anchoring of gene expression changes during estrogen-induced uterine growth. Environ Health Perspect 112:1589–1606.

Paules R. Phenotypic anchoring/linking cause and effect. 2003. Environ Health Perspect 111:A338–A339.

Schmidt CW. Critical care: applying genomics to inflammation outcomes. Environ Health Perspect 113:A816–A821.

Waters MD, Fostel JM. 2004. Toxicogenomics and systems toxicology: aims and prospects. Nat Rev Genet 5:936–948.

Younossi Z, Baranova A, Ziegler K, Del Giacco L, Schlauk M, Born T, et al. 2005. A genomic and proteomic study of the spectrum nonalcoholic fatty liver disease. Hepatology 42:665–674.

Note from the Editor: Good Bye and Thank You

Environmental Health Perspectives (EHP) is like one of the lighthouses that dot the North Carolina coast; the journal acts as a beacon warning people of potential environmental dangers and, at the same time, welcomes people whose goal is to improve global health. Although we report areas of concern about how our environment can negatively affect us, we also provide information that can give a sense of hope for the improvement of human health. Regardless of the information to be shared, EHP tries to provide the balance between voices that sometimes have competing interests.

I will be retiring at the end of December and have been blessed to have a fulfilling career dating back to 1969 that allowed me to experience industrial, academic, and governmental service. Along the way I have had the honor to work with many wonderful people. However, none of my experiences has been more fulfilling than my time at NIEHS during which I served with the National Toxicology Program and now with EHP. The talent, energy, tenacity, and altruism of these wonderful people are beyond compare.

NIEHS has been the benevolent sponsor of EHP since its inception over 30 years ago. NIEHS is an exceptional institution with exceptional people, who are at the forefront of research in environmental health issues. During this time EHP has given a voice to the institute and to the field of environmental health.

Although the future sponsorship of EHP is uncertain, the journal will continue in its mission of serving “as a forum for the discussion of the interrelationships between the environment and human health by publishing in a balanced and objective manner the best peer-reviewed research and most current and credible news of the field.”

My immediate plans are to go on extended camping trips across the United States with my wife, Marilyn (who is not just another pretty face!). I hope to use this time to contemplate new ways to contribute to scientific capacity building and information dissemination in the developing world, which has been my passion at EHP. I am very grateful for, and will always remember, the support and dedication of the EHP staff and the NIEHS administration during my tenure.

Thomas J. Goehl
Editor-in-Chief, EHP
National Institute of Environmental Health Sciences
National Institutes of Health
Department of Health and Human Services