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Toxicogenomics and toxic torts

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One of the first practical applications of toxicogenomics will probably be in the context of toxic tort personal injury litigation. Gene expression changes that 'fingerprint' exposure to particular classes of toxic substances can potentially be used to demonstrate exposure, prove causation and support novel damage claims in lawsuits brought by citizens injured by toxic exposures. Although the potential use of toxicogenomic data in toxic tort litigation is immense, there is a danger of premature use of such data before they have been adequately validated and characterized.

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Toxicogenomics is the study of the response of the genome to toxic agent exposure; it has been described as 'a tool of unprecedented power' in toxicology [1]. The term 'toxicogenomics' in its broadest meaning encompasses profiling of gene expression, protein composition (proteomics) and the metabolic constituents (metabonomics) of a cell. A key toxicogenomic technique is to profile (using a DNA microarray or 'gene chip') the

cell-wide changes in gene expression following exposure to toxins. This approach creates the potential to provide a molecular 'fingerprint' of exposure or toxicological response to specific classes of toxic substances [1–3].

Gene expression changes measured by DNA microarrays can provide a more sensitive and characteristic marker of toxicity than typical toxicological endpoints such as morphological changes, carcinogenicity and reproductive toxicity [4]. Moreover, altered gene expression can occur immediately following exposure, whereas the clinical manifestation of toxicity might take days, months or even years to develop. Initial 'proof-of-principle' experiments have successfully identified the category or toxicological mechanism of toxic chemicals on the basis of their gene expression profiles [3,5,6]. The potential promise of this technology is enormous. For example, DNA microarrays could be used to identify or confirm the category of toxic substances to which an individual was exposed, based on gene expression profiling.

Notwithstanding the tremendous potential of gene expression profiling, many obstacles and uncertainties remain to be resolved before toxicogenomic data should be used outside the research context for practical, regulatory or legal applications [7,8]. The toxicological significance of gene expression changes must be validated, including

an evaluation of the robustness of microarray results between or across different laboratories, species, individuals, tissues and time periods [4]. For example, it will be important to understand the time course of gene expression changes following toxic exposures because some alterations might be transient and others might lead to permanent changes.

One of the most difficult issues will be in differentiating gene expression changes that represent the adaptive response of cells to external stimuli that have no toxicological significance or increased risk from those gene expression changes that truly represent the early stages of disease progression [9]. For example, some changes in gene expression might simply represent a nonspecific and fully reversible response of the cell to stress or a response with no biological consequence. Given the massive quantity of data produced by a DNA microarray, there will almost certainly be many false positive results. There will also be difficult quality control and consistency issues with respect to data collection, storage, interpretation and display [2,4].

One of the first practical applications of toxicogenomics outside the research context will probably be in toxic tort litigation. A 'tort' lawsuit is one brought by a private citizen ('plaintiff') against another person or entity ('defendant') for compensation ('damages') of an injury allegedly caused by the defendant's wrongful act. When the wrongful act involves or results in exposure to a toxic agent, the case is classified as a 'toxic tort'. The plaintiff in a toxic tort lawsuit has to prove that the toxic exposure resulting from the defendant's act caused his or her injuries. The fair and reasonable resolution of such lawsuits is hindered by the numerous uncertainties and difficulty in proving whether a specific toxic exposure caused a particular plaintiff's disease. Consequently, many victims harmed by toxic substances are denied fair compensation for their injuries, whereas some apparently innocuous products (e.g. Bendectin and silicone breast implants) have been forced off the market by unwarranted liability.

Toxicogenomics has the potential to make toxic tort litigation more objective, fair and efficient. Just as forensic DNA evidence has helped to indict guilty criminals and exonerate innocent suspects, toxicogenomic data have the potential both to help injured victims recover damages and to assist innocent companies in defending against liability. At the same time, this new technology will present major evidentiary challenges for judges and juries.

There are no reported toxic tort cases to date in which toxicogenomic data have had a significant role. Legal commentators have, nevertheless, begun to focus on potential tort applications of genomic techniques [10–13]. These potential applications include using gene expression data to demonstrate exposure, to prove causation and to recover novel types of damages, such as for increased risks than have not yet manifested into symptomatic disease ('latent risks'). Using analogous precedents from US case law, these

potential uses of toxicogenomics in toxic tort litigation are discussed in the following section.

Demonstrating exposure

Injured plaintiffs have to prove that exposure to a defendant's toxic agent is sufficient to cause their illness. In many cases, such as those involving contaminated groundwater, pesticide use or air pollution, direct quantitative evidence of exposure is lacking, often resulting in the case being dismissed. Toxicogenomics could assist plaintiffs in demonstrating exposure or could support the defendant's counter-argument that there was no significant exposure. Gene expression assays of the plaintiff's blood or skin cells might demonstrate the presence (or absence) of gene expression 'fingerprints' that are characteristic of the class of toxic substances to which that person was allegedly exposed. If adequately developed, such an assay could quantify the level, or even the duration, of a plaintiff's exposure.

This application would obviously raise many evidentiary questions. For example, how well characterized and validated is the gene expression 'fingerprint'? How specific and sensitive is the gene expression profile with respect to the toxic agent at issue? Are the gene expression changes in the easily assayed tissues such as blood or skin cells representative of the changes in the less accessible tissue in which the disease actually occurs? Can other potential sources of exposure to that same toxic substance (or to other substances that cause similar responses) be excluded? What is the quantitative relationship between the level of exposure and the magnitude of the gene expression changes? Over what range of exposure is this relationship valid? Do inter-individual differences in susceptibility (genetic or non-genetic) affect gene expression patterns in different individuals? How does gene expression vary with single, acute exposures versus long-term chronic exposure? What is the time course of the gene expression changes following toxic exposure, and are these changes transient or long-term (Box 1)? Notwithstanding these important uncertainties and limitations, gene expression changes assayed using DNA microarrays could provide more informative and objective evidence of exposure than is typically available in toxic tort litigation.

Proving causation

Toxic tort plaintiffs must prove that their exposure to a toxic substance caused their illness. Legal causation in toxic tort cases has two elements. The first is general causation, which addresses whether the toxic substance produced by the defendant is capable of causing the health effect incurred by the plaintiff. Second, specific causation asks whether the toxic agent did, in fact, cause the health effect in that specific plaintiff. Toxicogenomic data could be relevant to both steps of the causation analysis.

With respect to general causation, most courts have insisted that the only relevant data are those involving both the precise toxic agent and exact health effect

Box 1. Temporal dimension of genetic changes

Litigation over the 1979 Three Mile Island (TMI) nuclear accident demonstrates the importance of the temporal dimension for genetic biomarkers of exposure. A class of residents living near the facility filed a lawsuit claiming that they developed cancer as a result of an alleged radioactive plume released during the accident. However, they lacked direct evidence to prove or quantify their radiation exposure [a]. The plaintiffs attempted to demonstrate their exposure based on an increased frequency of dicentric chromosomes in their lymphocytes, arguing that these genetic changes represented a quantitative biomarker of radiation exposure. The Court of Appeals held that the use of such genetic markers is a 'valid and reliable scientific methodology' for quantifying exposure but that its 'validity and reliability decrease as the time gap between the alleged irradiation and the dicentric count increases'. The court found that dicentric chromosomes could only provide an accurate indicator of dose within one or two years of exposure, and thus the plaintiffs' dicentric chromosome levels assayed 15 years after the TMI accident were no longer a reliable measure of exposure. In the same way, the time that lapses between exposure and measurement of gene expression changes in an exposed person will be a crucial factor in determining the validity, and hence admissibility, of such evidence.

Reference

a *In re TMI Litigation*, 193 F.3d 613 (3d Cir. 1999), *cert. denied*, 120 S.Ct. 2238 (2000)

involved in the case. Thus, courts have generally been unwilling to allow plaintiffs to rely on evidence showing that the same chemical can cause other comparable diseases. For example, a plaintiff with brain cancer will often be precluded from relying on evidence that the same chemical causes liver tumors or leukemia. Similarly, plaintiffs have been precluded from relying on evidence showing that structurally related or similar chemicals can cause the same health effect for which they have been diagnosed.

Given that most toxic substances have not been tested for many toxicological end points, data will be lacking for most specific chemical-endpoint combinations, even if some of these combinations involve a true causal association. Toxicogenomic data might be able to provide the necessary missing link in such cases and prove the absence of such linkages in other cases. For example, a study showing that the toxic substance to which the plaintiff was exposed produces a gene expression 'fingerprint' characteristic of chemicals known to cause the health effect from

which the plaintiffs suffers might be probative of general causation in the absence of any data directly linking the specific chemical and health effect. This type of evidence will no doubt be controversial and subject to severe challenges by the opposing side but nevertheless, might, at least in some cases, provide the missing link that plaintiffs need to establish general causation. Conversely, a defendant might be able to use toxicogenomic data to show that its product does not produce a gene expression profile consistent with the plaintiff's disease to rebut general causation (Box 2).

Toxicogenomic data could also be relevant to specific causation, in which a plaintiff must prove that the toxic exposure did, in fact, cause his or her disease.

'Particularistic' data showing that a specific individual's disease was caused by a particular exposure is extremely rare, if not non-existent, using current toxicological methods [14]. Applying toxicogenomics, a plaintiff could assay for changes in gene expression in his or her cells that are characteristic of the specific agent produced by the defendant. The types of gene expression changes that would be most relevant are not those of the initial cellular response to toxic agent exposure but the subsequent gene expression changes that are typical of the progressing disease process. In other words, the gene expression changes potentially relevant to the causation inquiry must go beyond those simply showing the fact of exposure and also represent genetic changes that are indicative of a disease process. Such evidence directly linking the toxic agent with the disease process in the individual plaintiff is likely to be highly persuasive to judges and juries. By analogy, the scientific experts who testified on behalf of silicone breast implant recipients claimed that specific antibodies found in some women with silicone breast implants provided a biomarker connecting leaking silicone with the development of disease. This testimony was highly influential to jurors, who awarded large damages to plaintiffs, even though these antibody tests were subsequently found to be invalid and unreliable [10,15].

Box 2. Disproving causation

A corporate defendant successfully used the absence of a genetic biomarker to defend against liability in a case in which the family of a deceased worker alleged that occupational exposure to benzene caused the worker's acute myelogenous leukemia (AML). The defendant did not dispute that benzene is capable of causing AML, but instead argued that benzene only causes the types of AML that have specific cytogenetic markers – breaks in the fifth and seventh chromosomes. The jury found in the defendant's favor based on the lack of such specific genetic changes in the cells of the deceased worker [a]. A different court rejected the same argument a few weeks later as 'nothing more than an untested, unsupported hypothesis cloaked in the aura of scientific knowledge' [b]. The presence or absence of gene expression changes could provide an even more specific and common genetic biomarker of causation than the chromosomal aberrations involved in these benzene cases, but the use of toxicogenomic data for such a purpose is also likely to be highly controversial. As greater understanding of the roles of specific genes in the toxicological response to particular toxins develops, however, toxicogenomic data showing changes in the expression of those genes will provide an increasingly informative and reliable marker of causation.

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 b *Lavender v. Bayer Corp.* (W. Va. Cir. Ct.No. 93-C-226-K, May 29, 1998)

Recovery for latent risks

The traditional rule in tort law is that 'the threat of future harm, not yet realized, is not enough' [16]. Notwithstanding this admonition, in recent years plaintiffs exposed to hazardous substances have increasingly sought recovery for latent risks that have not yet manifested into clinical disease. Such claims usually seek damages for the increased risk of future disease, recovery for the present fear associated with the increased risk, or costs for periodic medical monitoring [17].

To prevent a flood of latent risk claims, while also providing the possibility of recovery for the most compelling cases, courts have imposed threshold requirements for such claims. For example, most courts require proof of a 'present injury' for most increased risk and fear of disease claims, as well as a demonstration (and often quantification) of a sufficient quantum of

Box 3. Defining 'present injury'

A threshold requirement for recovery for a latent risk is that the plaintiff must have incurred a 'present injury'. Courts differ in the extent of impact that is necessary to meet this requirement. A few courts have taken the position that the mere fact of exposure is sufficient to establish a 'present injury'. Thus, the Tennessee Supreme Court has held that 'ingest[ing] an indefinite amount of a harmful substance' is itself a 'physical injury' [a].

Other courts have required evidence of an adverse physiological change as a result of the exposure, even if such changes occur at the subcellular level and are without detectable symptoms. For example, one court held that chromosome damage inferred from radiation exposure can be a 'physical injury' [b]. Finally, other courts have required 'an objectively verifiable functional impairment' before a present injury is recognized [c]. Gene expression changes associated with toxic exposures could span the range from adaptive responses to exposure with no toxicological significance, to subcellular manifestations of toxicity not associated with clinical symptoms, to changes that are associated with a functional impairment. The relevance of gene expression data associated with such changes will depend on how the reviewing court construes the term 'physical injury'.

References

- a *Laxton v. Orkin Exterminating Co.*, 639 S.W.2d 431 (Tenn. 1982)
- b *Brafford v. Susquehanna Corp.*, 586 F. Supp. 14 (D. Colo. 1984)
- c *In re Hawaii Federal Asbestos Cases*, 734 F. Supp. 1563 (D. Hawaii 1990)

increased risk [17,18]. Most plaintiffs exposed to hazardous substances are currently unable to meet these threshold evidentiary requirements, although some courts permit chromosomal or other subcellular changes to be inferred from exposure (Box 3).

Gene expression data could help many plaintiffs trigger recovery, by demonstrating both an existing 'injury' and a sufficient increase in risk. By providing a highly sensitive and specific marker of a toxicological response, microarray data could provide adequate demonstration of a present physical injury. A crucial issue will involve distinguishing gene expression changes that are merely adaptive responses from those that truly represent disease pathology (Box 3). Likewise, gene expression data might provide objective empirical evidence of increased risk, which might satisfy the requirement that the plaintiff demonstrates a sufficiently enhanced risk.

Plaintiffs at risk from exposure to hazardous substances might also seek compensation to conduct periodic medical monitoring using DNA microarrays to evaluate their disease status and progression. To recover medical monitoring costs, most courts

require: (1) that plaintiffs demonstrate a significantly increased risk of contracting a serious latent disease; (2) that this increased risk makes periodic diagnostic medical examinations reasonably necessary; and (3) that the monitoring and diagnostic methods used make early detection and treatment of the disease both possible and beneficial [19]. Gene expression assays could provide a more informative assessment of pre-clinical disease progression than currently available medical tests for many latent conditions. This assessment has the potential to greatly expand the number of potential medical monitoring claims, and will force courts and legislatures to confront the policy implications of this new type of liability.

Conclusion

As the cases discussed above demonstrate, several doctrinal templates for the application of toxicogenomic data to toxic tort litigation already exist. The use of gene expression data within these existing legal frameworks has the potential to make the resolution of toxic tort litigation more scientifically objective, fair and efficient. Plaintiffs might use these data to demonstrate exposure, causation or latent risks, and defendants could use the same type of data to refute such assertions.

There are many scientific [7,8] and legal [11,13] issues relating to the validation, quality control and significance of toxicogenomic data that remain to be addressed before the data should be applied in a non-research context. Toxic tort litigants have very little incentive to wait for these uncertainties to be fully resolved because, unlike scientists or regulators who have the luxury of revisiting their decisions, litigants are one-time players in a high-stakes game. Therefore, there will be temptation to use toxicogenomic data in toxic tort lawsuits prematurely, just as has occurred in the past with other types of novel scientific evidence [10]. The US Supreme Court recently held that trial judges must serve as scientific 'gatekeepers' to ensure that scientific evidence admitted into evidence is both 'reliable' and 'relevant' [20]. Toxicogenomic data are certain to provide a new challenge for this gatekeeping role, probably much sooner than most lawyers and scientists realize.

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