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GENE PROFILING: IMPLICATIONS IN DERMATOLOGY

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Summary

DNA microarrays are capable of following the level of expression of, virtually, all genes in a human tissue. This has been employed to determine the aberrant gene expression profiles in many skin diseases, including ultraviolet light damage, inflammatory processes and cancers. Because of its accessibility, skin also served as one of the initial targets of basic research using DNA microarrays. Both the epidermis and dermis have been extensively investigated. Development of bed-side uses of DNA arrays, and the concomitant price reduction of the materials and methods of microarray analyses, holds great promise for improved diagnosis, treatment and prevention of dermatologic disorders.

Keywords

cytokines; DNA microarrays; melanoma; psoriasis; transcriptional profiling; UV light

A **microarray** is an ordered arrangement of nucleic acids, proteins, small molecules, carbohydrates etc., on solid supports, which enables large-scale analysis of complex biochemical samples. A **DNA chip** is a microarray that consists of sequences from thousands of different genes arrayed at fixed locations on supports, usually glass microscope slides, silicon chips or nylon membranes. The DNA is printed, spotted, or directly synthesized on the support. There are five steps in a gene profiling microarray experiment: 1. Prepare (or buy) the DNA chip with the target genes. 2. Generate a biological sample containing a mixture of fluorescently labeled cDNAs. 3. Hybridize the mixture of labeled cDNAs with the DNA chip. 4. Detect and measure the bound cDNAs using laser technology; store data in a computer. 5. Analyze data using computational methods.

The technology has made possible comprehensive and systematic comparisons of all genes expressed in a given tissue or cell type, and has already proven extremely useful in basic research as a hypothesis generating and data accumulating tool. However, its full potential

will be realized with its uses at the bedside. It will be used for disease classification and sub-classification (cancers, wounds), severity and prognosis (e.g. estrogen dependent *vs.* independent breast cancer; healing *vs.* non-healing diabetic foot ulcer), for choosing the appropriate treatment (e.g., disease is responsive to drug A, not B) and early detection (for example, Alzheimer's and Post-traumatic Stress Disorder have characteristic "signatures" in blood). This technology will lead to customized treatments tailored to individual patients.

Skin is the most accessible target for testing new treatments of human diseases, from topical medications for local cutaneous symptoms, to patches that treat systemic problems and even to gene therapy. Because of its accessibility, skin has been among the first organs analyzed using DNA microarrays (1) (2). Melanomas, basal and squamous cell carcinomas have been intensely investigated using gene profiling, as well as psoriasis, keloid formation etc. Importantly, the RNA from the skin surface can even be recovered using tape stripping, an easy, non-invasive procedure; this RNA is of suitable quality and quantity for gene profiling (3). However, skin samples from patients, while potentially very informative, must address differences in proportions of various cell types (4), age and body sites of the sample origin, and issues even more difficult to standardize, such as history of sun exposure, presence of underlying disease, lifestyle, nutrition etc.

To avoid some of the confounding effects, many researchers have focused on monocultures of cutaneous cells, keratinocytes, fibroblasts and melanocytes, or cell lines derived from these cells. In particular, epidermal keratinocytes have been the target of many studies because they respond to a rich variety of inflammatory and immunomodulating cytokines, hormones, vitamins, UV light, toxins and physical injury.

Among of the first dermatologically relevant studies using microarrays was the analysis of the effects of serum on dermal fibroblasts (2). Unanticipated, serum-treated fibroblasts initiated a wound healing response. Serum is present in the dermis only after wounding and the fibroblast interpreted its presence of serum as a signal that injury occurred. While the induction of individual wound healing response proteins could have been detected using classical molecular biology methods, only microarray analysis could provide the comprehensive global overview of the new and exciting role of fibroblasts in serum-induced wound repair.

Many microarray studies followed, focused on skin cancers, inflammatory diseases, epidermal differentiation, stem cells etc. These were reviewed recently (5) (6) (7). DermArray, a skin-specific cDNA array containing >4000 genes is commercially available (8), and keratinocyte-specific house-keeping genes have been identified (9) (10). The accumulation of large volume of bioinformatics data relevant to skin led us to coin the term Skinomics (11).

The epidermis is our first line of defense from **ultraviolet light** (UV), the major environmental carcinogen that targets skin almost uniquely. Therefore, we and others used microarrays to analyze the transcriptional effects of UV light in human epidermal keratinocytes (12) (13) (14) (15) (16). The microarray results show that keratinocytes respond to UV light by inducing a cell repair program to repair themselves from the damage,

but they also act to protect the underlying organism. The early changes in gene expression induce transcription factors, signal transducing, and cytoskeletal proteins that generate a “paused” phenotype, presumably, to allow for the assessment of damage and initiation of repair. Later, keratinocytes produce secreted signaling proteins, cytokines and chemokines, to alert the surrounding tissues to the UV damage. Still later, components of the cornified envelope are produced to enhance the stratum corneum while simultaneously terminally differentiation removes a carcinogenic threat (12).

Importantly, the results from several laboratories were virtually identical, despite the differences in experimental approaches, countries of origin or experimental time-frames (12) (13) (14) (15) (16). Interestingly, like in the parable of the blind men and the elephant, different researchers emphasized different aspects of the results. For example, Li et al. focused on the metabolic effects and epidermal differentiation, Sesto et al. on DNA repair, Howell et al. focused on angiogenesis, Murakami et al. on oncogenes. The large amounts of data provided by microarrays allow researchers to demonstrate individual preferences, interests and inclinations.

Enk et al. have expanded these studies to UV-irradiated skin in human volunteers (17) (18). In general, the responses in the two systems were quite similar, although the DNA repair proteins seem more responsive to UV irradiation *in vivo* than in cultured cells. The differences may be largely due to the contribution of the cells from the differentiating, upper layers of the epidermis, which are absent from monolayer keratinocyte cultures.

Melanoma is, unfortunately, among the most aggressive human cancers and its incidence is increasing. Because of its deadliness, melanoma was among the earliest targets of DNA microarray studies (19). Melanoma diagnosis and natural history have received a great amount of attention by the microarray researchers. Studies compared healthy melanocytes to melanoma cells and examined the differences between cell lines that differ in metastatic potential (1, 20) (21) (22) (23) (24) (25) (26) (27) (28) (29) (30). These studies showed that some of the differentially expressed genes are, unsurprisingly, encoded in the chromosomal regions commonly altered in melanomas. Osteopontin was identified as a consistently overexpressed marker of early invasive melanoma. Several groups used laser capture microdissection to compare the transcriptomes of pigmented moles, primary melanomas and melanoma metastases. Interestingly the metastatic samples exhibited two distinct patterns of gene expression, similar to the microdissected flat vs. nodular components of large primary melanomas (22).

The significant progress made suggests that soon we can expect to have molecular markers of melanoma progression, diagnostic tools that can predict its severity and even genetic markers that may be able to identify the individuals particularly at risk. These advances will not only lead to earlier diagnosis and more effective treatments, but also to the development of tools to prevent this deadly cancer.

Psoriasis, a chronic inflammatory skin disease affecting approximately 2% of the population, is environmentally triggered, but depends on genetic risk factors. Two groups, one in New York, the other in Saint Louis, separately and in cooperation, lead the gene

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profiling research on psoriasis (31) (32) (33) (34) (35). A large number of genes that distinguish between the involved psoriatic skin and uninvolved or healthy skin have been identified; these genes that molecularly define psoriasis. Many of the genes in this set mapped to the known psoriasis susceptibility loci (33). A subset of genes that changed significantly in response to therapy have been characterized; many of the demonstrated changes preceded actual clinical improvement (31). An remarkable *in silico* analysis, followed up by lab-bench experiments, identified a large set of psoriasis-associated genes and even a set of genes expressed at high levels only in distal, uninvolved skin of psoriasis patients (36). This study illustrated the power of bioinformatics and the wealth of data already amassed by the researchers using microarrays to study skin.

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Several cytokines and growth factors have been linked with psoriasis, including IL-1, IL-12, TNF α , Interferon- γ and Oncostatin-M, and the effects of these signaling proteins on epidermal keratinocytes have been extensively studied (34, 37–42). To define TNF α action in epidermis, we compared the transcriptional profiles of untreated normal human keratinocytes to those treated with TNF α (40) (43). We found that TNF α regulates not only immune and inflammatory responses but also tissue remodeling, cell motility, cell cycle, and apoptosis TNF α promotes tissue repair by inducing basement membrane components and collagen-degrading proteases, as well as integrins and actin cytoskeleton regulators, enhancing keratinocyte attachment and motility. IFN- γ is an antiviral cytokine with multifunctional, cell type-specific immunomodulatory activities, implicated in diseases ranging from psoriasis to warts and cancer. In keratinocytes, IFN- γ induced tight junction proteins, which could deny viruses paracellular routes of infection, suppressed keratinocytes differentiation markers, presumably to interfere with papillomaviruses, which require differentiating cells for growth, and also suppressed the expression of over 100 genes responsible for cell cycle, DNA replication and RNA metabolism, thereby shutting down many nuclear processes and denying viruses a healthy cell in which to replicate (42). In addition, IFN- γ induced HLA, proteasome and cell adhesion proteins, facilitating leukocyte attraction and antigen-presentation by keratinocytes. In summary, IFN- γ initiates a well-organized molecular program boosting host antiviral defenses, obstructing viral entry, suppressing cell proliferation and impeding differentiation. Oncostatin-M plays an important role in inflammatory and oncogenic processes in skin, including psoriasis and Kaposi sarcoma. We found that Oncostatin-M strongly and specifically affects the expression of genes involved with innate immunity, angiogenesis, adhesion, motility, tissue remodeling, cell cycle and transcription (37). The primary targets of OsM regulation are secreted cytokines and growth factors and their receptors, as well as nuclear transcription factors. On the other hand, our studies focused on transcriptional profiling of anti-inflammatory agents, corticosteroids, revealed that in addition to known TNF α and IL-1 inhibitory effects, corticosteroids block activation of IFN- γ pathway (44). Furthermore, the anti-inflammatory effects of corticosteroids have timed responses: anti-TNF α is the earliest (first hour), followed by anti-IL1 (24 – 48 hours) and anti-IFN- γ (72 hours). Furthermore, corticosteroids act as anti-apoptotic agents and prevent UV-mediated apoptosis.

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Atopic dermatitis (AD) is a disease similar to psoriasis, but with a distinct clinical course. For example, skin infections are common in AD, but not in psoriasis. Because of their similarities, AD and psoriasis were compared using microarrays in a series of studies (45)

(46) (47) (48) (49). The expression of innate immune response genes, human beta defensin-2, IL-8, and inducible NO synthetase was found to be decreased in AD, when compared with psoriasis, and many antimicrobial proteins were found overexpressed in keratinocytes from psoriatic but not in AD skin. These findings could explain the increased susceptibility of AD skin to infection.

Keloid fibroblasts showed a constitutive increase in NF κ B transcription factor activity in comparison to normal skin (50) (51) (52) (53). Interestingly, the transcription profile of keloids fibroblasts resembles that of their chondrocyte-osteoblast cousins. Therefore, the fibroblast in keloids may have reverted from their dermal phenotype to one less differentiated, perhaps through activation of the NF κ B signaling pathway.

As a complex, multi-step process involving highly coordinated, interacting regulatory pathways, **wound healing** is well suited for study by microarray technology (54) Reports in literature have used small scale cDNA arrays to characterize the transcriptional profile of skin repairs (55). Nevertheless, these pioneer papers represent the major step forward in understanding how various wounds heal. Recently, we have shown that microarrays can also be utilized as a diagnostic tool during surgical debridement of chronic (non-healing) wounds. Non-healing edge of a chronic ulcer has specific, consistent and recognizable signature whereas edge upon successful debridement also has its own reproducible signature profile. Thus, microarray profiling can be used as a guiding tool during surgical procedure (4).

Dermatology was among the first medical disciplines to embrace and benefit from the microarray technology. There is a dedicated core of skin biology researchers who are working hard to apply the benefits obtained through this methodology to the patients' bedsides, and, as importantly, making great strides made toward increased understanding of the basic biology of healthy human skin.

We can soon expect diagnostic and prognostic tools for melanoma and for other cutaneous neoplasms, as well as for the inflammatory diseases of skin. Molecular effects of UV have been already characterized; comprehensive molecular and mechanistic details of wound healing will shortly follow. The epidermal differentiation process will shortly be fully characterized at the transcriptional level. Epidermal stem cells are beginning to yield their secrets and new knowledge and understanding of their biology will follow. In the near future, the less abundant, although not less important, cell types will also become a target of bioinformatics. Inherited genodermatoses, including complex multigenic disorders, will be genetically mapped and the transcriptional effects of the mutations that cause them will be identified. The increased knowledge and understanding of skin diseases will lead to improved therapies. Moreover, we may be able to enhance the function of healthy skin, to prevent skin aging and, important in dermatology, achieve cosmetic advances as well. If all this sounds overoptimistic, I would like to point out that the microarray methodology is less than a dozen years old and that its achievements will most likely surpass even the wildest predictions.

How will this change the practice of medicine and dermatology in particular? With little imagination we can see the clinic of the future:

A patient comes in. In addition to taking the blood pressure and pulse, the nurse collects a blood sample and, specifically in a dermatologists office, using a tape-stripping device, painlessly collects a skin sample. From the blood, patients genomic DNA gets analyzed to identify any genetic disease or any inherited predispositions for genetic diseases. Also, RNA from blood cells gets analyzed using transcriptional profile microarrays, identifying latent, possible underlying diseases, such as infection, inflammation, metabolic imbalances etc. From the data, treatment options are suggested; their efficacy will be monitored using microarrays.

Specifically in dermatology, tape-stripping sample gets analyzed and potential underlying diseases are investigated. For example, skin flora and especially infectious agents are identified. HPV, if present, is quickly genotyped. Next, psoriasis, AD other inflammatory diseases are characterized and typed. Tumors and benign lesions are identified, carcinomas or melanoma, if present, are typed and sub-typed, their prognosis evaluated and treatment options suggested - all based on characteristic gene expression patterns. Chronic ulcer type (diabetic, venous, pressure etc.) and subtypes (with or without neuropathy) are identified, microarray-guided debridement is performed along with analyses for presence of a non-healing gene signature, which leads to customized choice of therapy.

Expert Commentary: Microarrays offer tremendous potential for enhanced understanding of the healthy and pathological processes in skin. It has been adopted by many research laboratories and applied to serious dermatologic problems, including cancers, psoriasis etc. The increased understanding will lead to identification of targets for treatment and, hopefully, more effective drugs with fewer side effects. However, the methodology is still in its infancy, not ready for clinical applications. It will be expanded to the areas not currently under study. New data analysis methods will make the research easier and more efficient.

Five-year view: Currently, the microarray analysis is in its lab-bench, exploratory phase. New arrays are currently at early stages of development; they address specific exons of differentially spliced genes, target miRNAs or cover the entire genome in search of disease-associated polymorphisms and mutations. However, at the moment they have been applied in skin research only to a very limited extent. Because of its promise, very soon it will be developed for the clinic, where it will have major impact on diagnosis and treatment. Dermatology, given the easy accessibility of the affected tissue, is poised to exploit the power of microarrays quickly and efficiently. In 5 years, first microarrays will appear in dermatology practice. Soon afterwards, it will become a fully accepted, standard methodology.

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Key issues

- Microarrays represent a tremendous promise for clinical medicine, and particularly for dermatology.
- Important dermatologic diseases, including melanoma, psoriasis, UV damage, have been the early targets applying microarray studies in research.
- The effects of proinflammatory cytokines in the epidermis have received significant attention.
- Currently, the high price and complex methodology preclude the widespread use of this technology.
- Inconsistent and inefficient data analysis software needs significant improvement, before microarrays are fully accepted by the research and medical communities.
- Establishment of a skin-focused electronic bioinformatics databank would represent a major boon for the use of microarrays in dermatologic research and practice.