Gene Expression Profiling for Melanoma Prognosis: Going Beyond What We See With Our Eyes

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Dermatology certainly is the most visual medical specialty. In the current era of powerful electronic imaging and laboratory techniques, the skills of physical diagnosis seem to have become less important in medicine—not so in dermatology, in which the experienced clinician is able to identify many conditions by simply looking at the skin. Of course, dermatologists do heavily rely on dermatopathologists to microscopically visualize biopsies to distinguish diseases. Even as we acknowledge the dominant role of visual recognition, there is increasing progress in making clinical determinations based on molecular events. The era of genomic dermatology is here.

The Genodermatoses

There are more than 500 dermatologic conditions resulting from heritable mutati onal events.[1] The rarity of most of these diseases and variability in phenotypic manifestations presents considerable diagnostic challenges, typically the province of a select group of clinical pediatric dermatologists whose abilities have been developed by experience.[2] However, the addition of genomic analysis has now made reliable identification more accessible to a wider group of clinicians.[3] The Human Genome Project was arguably the most successful health policy endeavor in human history, promoting the development of massive automated, information theory–driven applications to analyze DNA sequences.[4] We all think of DNA analysis as the ultimate means to detect mutations by sequencing whole exomes—and in fact the entire genome of affected individuals searching for mutations—but DNA sequencing often is insufficient to detect mutations in noncoding regions of genes and to identify abnormalities of gene expression (eg, splice variants). Building on the advances in high-throughput nucleic acid sequencing and massive computerized analysis, the field has now taken a quantum leap further to sequence transcribed RNA to detect abnormalities.[5]

The techniques are straightforward: RNA is isolated and reverse transcribed to complementary DNA. The complementary DNA is amplified and then processed by high-throughput sequencers. The sequences are then identified by computer algorithms. It is possible to fully define the transcriptomes of multiple genes, even reaching the threshold of resolution of gene expression emanating from a single cell.[6]

Studying Gene Expression for Malignant Melanoma

As much as we rely on visual interpretations, we acknowledge that many conditions look very similar, whether to the naked eye or under the microscope. This is true for rare diseases but also for the rashes we routinely see. A group of investigators recently used RNA transcriptome sequencing to analyze differences between atopic dermatitis and psoriasis, permitting better differentiation of these 2 common conditions.[7]

One of the greatest challenges confronting dermatologists and their dermatopathologist partners is to distinguish malignant melanoma from benign nevi.[8] Despite staining for a number of molecular markers, some lesions defy histopathology, such as distinguishing benign and malignant Spitz nevi; however, recent work on RNA transcriptomes suggests that gene expression may increase confidence in assessing atypical Spitz nevi.[9] A 23-gene expression panel has yielded a sensitivity of 91.5% and a specificity of 92.5% in differentiating benign nevi from malignant melanoma.[10]

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From the Research Laboratory to Routine Clinical Use

Undoubtedly, it is a large step from proof-of-concept studies to accepted clinical use. The ultimate achievement for a laboratory technique is to enter approved clinical use. Gene expression panels have now been approved by numerous third-party insurers to help predict future clinical evolution of biopsied melanomas. Although early in situ melanomas are eminently curable by wide excision, lesions that have more concerning characteristics (eg, depth >0.8 mm, ulceration) may progress to metastatic disease. The gratifying success of checkpoint inhibitor therapy has improved the previously dismal outlook for advanced melanomas.[11] Dermatologists search for clues to suggest which patients may benefit from adjuvant therapy. Sentinel lymph node biopsy (SLNB) has been a standard-of-care technique to help make this determination.[12]

It has now been demonstrated that gene expression array analysis can provide evidence complementing SLNB results or even independent of SLNB results. In extensive validation studies, a 31-gene expression panel analyzing initial melanoma biopsy specimens showed predictive value for later recurrence and development of metastatic disease.[13,14] The gene expression studies have identified patients with negative SLNBs who have gone on to develop metastatic melanomas.[15] It has been suggested that gene expression panel diagnosis may reduce the need for invasive SLNBs in patients in whom the surgical procedure may involve risk.[16]

Looking to the Future

The progress of science is the result of many small steps building on prior work. The terms *breakthrough* and *game changer* in medicine have been popularized by the media and rarely are valid. On the contrary, sequential development of methods over many years has preceded the acclaimed successes of medical research; for example, the best-known medical breakthrough—that of Salk's inactivated polio vaccine—was preceded by the use of an inactivated polio vaccine by Brodie and Park[17] in 1935. However, it was the development of tissue culture of poliomyelitis virus by Enders et al[18] that provided the methodology to Salk's group to produce their inactivated polio vaccine.

The ability to go beyond our visual senses will be of great importance in characterizing the variability of skin diseases, especially in skin of color patients; for example, acral melanoma is perhaps the primary melanocytic malignancy in darker-skinned patients and is the target of RNA transcriptomic research.[19] Progress is continuing on gene therapy for a growing number of skin conditions.[20,21] In vivo correction of abnormal genes is being attempted for a number of inherited cutaneous diseases,[22] notably for disorders of skin fragility.[23] For now, we welcome the addition of genomic capabilities to the visual practice of dermatology and the capability to go beyond that which we can see with our eyes.

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