Recessive Dystrophic Epidermolysis Bullosa–Associated Squamous-Cell Carcinoma: An Enigmatic Entity with Complex Pathogenesis

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Expression of either collagen VII or the noncollagenous (NC1) fragment derived from it has been suggested to be indispensable for the development of squamous-cell carcinomas (SCCs) in patients affected by recessive dystrophic epidermolysis bullosa (RDEB). This view is challenged here by the observation that SCCs do develop in RDEB patients lacking expression of collagen VII altogether. The aggressive behavior of RDEB-associated SCCs remains unexplained.

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The term epidermolysis bullosa (EB) represents a heterogeneous group of mechanobullous disorders characterized by skin fragility and blister formation. In addition to the skin, a number of other specialized epithelia, including the oral mucous membranes as well as those of the respiratory, vesicourinary, and gastrointestinal tract, can be affected (Fine *et al*., 1999). In milder forms of EB, blisters may be confined to limited areas of the skin, primarily the hands and feet. In contrast, in the most severe forms of EB, minimal trauma can result in widespread blistering and cutaneous erosions that heal slowly, if at all. The clinical course of the recessive dystrophic form of EB (RDEB, the Hallopeau–Siemens type; OMIM#226600) is unrelenting, and the affected patients develop severe mutilating scarring and are at high risk of developing squamous-cell carcinomas (SCCs) of the skin. Unlike sporadic SCCs in the general population, the RDEB-associated SCCs readily metastasize and have emerged as a prevalent life-threatening complication in these patients (Fine *et al*., 1999).

The cutaneous fragility in RDEB is caused by mutations in the COL7A1 gene, which encodes type VII collagen, a structural component of anchoring fibrils at the cutaneous basement membrane zone (Varki *et al*., 2007). Wild-type collagen VII contributes to the structural integrity of the basement membrane zone by tethering the *lamina densa* of the dermoepidermal basement membrane to the underlying papillary dermis (Shimizu *et al*., 1997). A wide spectrum of COL7A1 mutations that affect either collagen VII protein production or fibrillar assembly have been linked to DEB. In RDEB patients, premature STOP codons are frequently observed, predicting expression of truncated collagen VII, including the noncollagenous 1 (NC1) domain, but lacking C-terminal sequences necessary for collagen VII assembly. The molecular genetic hallmark of the most severe RDEB is STOP codon mutations in both alleles, spanning the entire length of the collagen VII polypeptide (Varki *et al*., 2007).

Ortiz-Urda and colleagues (2005) recently demonstrated that expression of the NC1 fragment was required for malignant transformation of a series of keratinocytes isolated from RDEB patients. In addition, they observed that expression of either full-length collagen VII or the NC1 fragment was necessary for tumorigenic conversion of normal keratinocytes from non-RDEB individuals. Pourreyron *et al*. (2007, this issue) revisited the requirement of collagen VII expression for SCC development in another series of SCC cell lines isolated from RDEB patients. They demonstrate that 2 of 11 patients investigated developed SCC in the absence of collagen VII or NC1 expression and conclude that, in RDEB patients, expression of collagen VII fragments is not a necessary requirement for SCC development. In support of this notion, we have identified in the DebRA Molecular Diagnostics Laboratory mutation database seven RDEB patients who were compound heterozygotes with two COL7A1 STOP codon mutations *in trans* upstream from the NC1/C7 junction (Varki *et al*., 2007). These patients are predicted not to express NC1, yet two of three, who were over 30 years of age, have developed aggressive SCCs (J. Uitto, unpublished observations).

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Can these seemingly contradictory results be reconciled? The answer may lie in the use of distinct experimental systems that were employed to assess malignant transformation. Ortiz-Urda *et al*. (2005) based their study on the use of an experimental model system to assess the tumorigenic potential of normal keratinocytes. To achieve tumorigenicity in immunodeficient mice, they retrovirally transduced normal keratinocytes with oncogenic Ras (Ha-Ras-V12) and the NF-κB inhibitor IκBα. Thus, expression of collagen VII appears to be an absolute requirement for tumor formation driven by Ha-Ras, leaving open the question of whether this observation can be generalized to RDEB patients. Pourreyron *et al*. (2007) resolve this question by demonstrating that expression of collagen VII or fragments thereof is not strictly required

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for SCC development in patients. Clearly, their findings must be confirmed in a larger cohort of RDEB patients afflicted with SCCs. However, their work highlights the importance of molecular epidemiology in patients to ascertain the relevancy of findings in experimental models of skin tumor development.

Of course, it is possible that the requirement of NC1 expression for SCC development is restricted to a subset of RDEB patients in which Ha-Ras mutations occur. In sporadic SCCs Ras mutations are infrequent and typically occur late in tumor progression (Campbell *et al.*, 1993; Clark *et al.*, 1993). Unfortunately, the activation state of Ha-Ras in RDEB-associated SCCs is currently unknown. If a high frequency of Ras mutations should be prevalent in RDEB-associated SCCs, it would be of interest to determine whether the tumors formed in the absence of collagen VII expression exhibit deregulated signaling pathways normally dependent on the presence of either collagen VII or the NC1 domain (Rodeck *et al.*, 2007). Regardless of the results of future efforts to resolve these issues, expression of the NC1 domain of collagen VII alone is not likely to provide a reliable diagnostic tool to identify patients at risk of SCC development. Instead, collagen VII joins a long list of extracellular matrix components that have been implicated in SCC development at the microenvironment of the tumor–host interface, including collagen IV, collagen I, fibronectin, and laminin 332 (formerly laminin 5) (Abelev and Lazarevich, 2006; Marinkovich, 2007). Much like these, collagen VII may act as a "modifier" of the transformed state by enhancing the malignant potential of initiated keratinocytes. Yet none of these extracellular matrix components is likely to be an absolute requirement for tumor progression.

RDEB, more so than less aggressive forms of EB, is characterized by chronic wound healing and excessive scar formation that last decades before SCCs are manifest. An interesting parallel to SCCs arising in continuously remodeling scar tissue is Marjolin's ulcers—SCCs that typically arise in burn scars many years after the initial scarring event (Phillips *et al.*, 1998). Interestingly, these SCCs are also very aggressive and invasive, much like RDEB-associated SCCs. These parallels raise the question of whether, regardless of collagen VII/NC1 expression status, chronic wound healing represents the driving force for the development of highly malignant SCCs in both the general population and RDEB patients.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Genital and Nongenital Nonmelanoma Skin Cancer: More Epidemiological Studies Are Needed

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Although black men in the United States have a lower mortality of nongenital nonmelanoma skin cancer (NMSC) than white men, they have a higher mortality of genital NMSC than white men. Mortality of NMSC has declined over time. Ethnicity-specific incidence and survival analyses of NMSC can be used to determine to what degree earlier detection and/or more efficient therapies have contributed to these observations.

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The burden of nonmelanoma skin cancer (NMSC) can be described by a variety of measures, including mortality. Although death among people with NMSC is the exception rather than the rule, detailed analyses of routinely collected mortality data provide important insights into the burden of disease. For example, although the age-standardized mortality rates of NMSC decreased in the territory

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