from 12 patients with recessive dystrophic epidermolysis bullosa. They show convincingly that susceptibility to developing invasive SCC, both clinically and experimentally, depends strictly on the retention of part of the collagen VII protein. Keratinocytes from patients carrying mutations that abrogate the deposition of collagen VII do not develop into invasive SCC, whereas those from patients with mutations that result in deposition of a crucial fragment of collagen VII do become cancerous.

Collagen VII is produced primarily by keratinocytes, with perhaps a small contribution from dermal fibroblasts. The collagen VII molecule has a characteristic central glycine-rich, triple-helical collagenous domain, with noncollagenous domains at its amino and carboxyl ends. Keratinocytes from patients with mutations that specifically leave intact the amino-terminal non-collagenous domain (NC1) of collagen VII, and more specifically the fibronectin III–like repeats within the NC1 domain (FNC1) that bind to laminin 5, developed into invasive SCC. Furthermore, introduction of either the NC1 or FNC1 domains into patient keratinocytes deficient in collagen VII restored a predisposition to tumorigenesis, whereas introduction of NC1 without the fibronectin repeats did not. Interestingly, antibodies that specifically recognized the FNC1 domain of collagen VII either prevented tumor development or suppressed tumor invasion when administered to mice with SCC tumors caused by Ras/IκB-transformed keratinocytes from normal individuals. Invasion studies in vitro confirmed the in vivo findings and further revealed that interaction of FNC1 with laminin 5 was required for the invasive phenotype to develop.

What do these results tell us about epidermolysis bullosa and SCC? First, they suggest an explanation for why chronic wounds seldom develop into SCC in patients with mutations in adhesion complex proteins that are closer to the epidermis (for example, laminin 5, hemidesmosomal proteins, and intermediate filament proteins). Keratinocytes harboring such mutations lack an intact adhesion complex between the NC1 domain of collagen VII and laminin 5 and the hemidesmosomes. Hence, these keratinocytes are not tethered to the dermis and may not receive the stromal signals that they would need to migrate to and invade the dermal layer. Laminin 5 is the ligand for $\alpha_6\beta_4$ integrin, a signaling receptor on the surface of basal keratinocytes. Hence, interactions between collagen VII and laminin 5 may be the conduit for stromal signals that direct the migratory and invasive behaviors of epidermal tumors (6).

Ortiz-Urda et al. also show that boosting production of NC1 enhances the invasiveness of transformed keratinocytes from normal individuals, and of keratinocytes from patients with other skin diseases. A central regulator of collagen VII expression is transforming growth factor–β (TGF-β) (7), which enhances invasion and metastasis of established squamous cell tumors and other epithelial neoplasms (8). The new work suggests that the relationship between collagen VII and TGF-β is worth exploring further. There are also two possible clinical applications of the current study. Attempts to restore collagen VII locally using gene therapy in patients with dystrophic epidermolysis bullosa are under active investigation (9). The authors caution that for certain patients, restoration of collagen VII containing the NC1 domain could increase their risk of developing SCC, particularly in those who lack production of collagen VII. On the other hand, the good news is that the NC1 domain could be a therapeutic target for treating invasive SCC and other cancers.

However, a therapeutic molecule that binds to the NC1 domain must block the molecular interactions required for tumor invasion while leaving intact those required for anchoring the epidermis to the dermis. We are faced with a possible Pyrrhic victory as we contemplate the epithelial-stromal interface: perhaps winning the battle against SCC but losing the battle against the disfiguring skin defects of dystrophic epidermolysis bullosa.

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EVOLUTION

Fossil Horses— Evidence for Evolution

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Thomas Huxley, an early advocate of Darwinian evolution, visited the United States in 1876 on a lecture tour. Huxley had planned to talk about evidence for evolution based on a fragmentary sequence of fossil horses from Europe. One of Huxley's first stops was at Yale, where he studied the fossil horse collection assembled by the paleontologist O. C. Marsh during expeditions to the western territories. Huxley was so taken with the definitive evidence provided by Marsh's fossil horse collection that he used this evolutionary sequence as the focal point for his subsequent talk to the New York Academy of Sciences (1).

Since the late 19th century, the 55-million-year (My) phylogeny of horses (Family Equidae)—particularly from North America—has been cited as definitive evidence of long-term "quantum" evolution (2), now called macroevolution. Macroevolution is the study of higher level (species, genera, and above) evolutionary patterns that occur on time scales ranging from thousands to millions of years. The speciation, diversification, adaptations, rates of change, trends, and extinction evidenced by fossil horses exemplify macroevolution.

The sequence from the Eocene "dawn horse" eohippus to modern-day Equus has been depicted in innumerable textbooks and natural history museum exhibits. In Marsh's time, horse phylogeny was thought to be linear (orthogenetic), implying a teleological destiny for descendant species to progressively improve, culminating in modern-day Equus. Since the early 20th century, however, paleontologists have understood that the pattern of horse evolution is a more complex tree with numerous "side branches," some leading to extinct species and others leading to species closely related to Equus. This branched family tree (see the figure) is no longer explained in terms of predestined improvements, but rather in terms of random genomic variations, natural selection, and long-term phenotypic changes (3).

The Equidae, a family within the odd-toed ungulate Order Perissodactyla (which includes rhinoceroses, tapirs, and other closely related extinct groups), consists of the single extant genus Equus. Depending upon interpretation, it also includes several subgenera, 8 to 10 species, and numerous subspecies (4). On the basis of morphological differences, Equus is separated into two or

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