BENCHSIDE DISPATCHES

By William Ju, MD

EPIDERMOLYSIS BULLOSA

WITH ANGELA CHRISTIANO, PhD

Welcome to the fifth installment of Benchside Dispatches. In this installment, Angela Christiano, PhD, discusses epidermolysis bullosa (EB). Dr. Christiano is the Richard and Mildred Rhodebeck Professor of Dermatology and Professor of Genetics & Development and Director, Basic Science Research Group of Dermatology at Columbia University College of Physicians & Surgeons. Her research focus is the study of inherited diseases of skin and hair, and a major objective of her laboratory is to develop innovative therapies through an advanced molecular understanding of disease pathogenesis.

Dr. Christiano has published extensively in the peer-reviewed literature, and her breakthrough work in EB can be found in journals including Science Translational Medicine, Nature Genetics, the Journal of Clinical Investigation, PNAS, and the Journal of Investigative Dermatology. She is on the board of trustees and scientific advisory board of DEBRA of America, and is the current President of the Society for Investigative Dermatology.

Epidermolysis bullosa is a family of rare skin blistering conditions that currently have no cure. EB can have devastating and even life-threatening sequelae, including the development of cutaneous squamous cell cancer associated with the most severe forms of dystrophic EB. Those that live with the condition can continually experience great discomfort and negative quality of life, as the current treatments are palliative in nature.

However, because of work in the field over about the past 25 years, the genetic underpinnings of EB have been elucidated. With that knowledge at hand, the race is on to find a cure—and thanks to the burgeoning field of molecular medicine, that goal is not as distant as it once was.

Angela Christiano, PhD, has been at the forefront of scientific and medical research into EB since the time of her postdoctoral fellowship in Dr. Jouni Uitto's lab, where she began her work in EB. Her laboratory at Columbia continues to provide critical and leading research. Her profound insights and discoveries continue to move the field forward both in fundamental understanding and for developing new treatments that can have substantial clinical impact.

William Ju, MD: How robust is our current understanding of EB?

Angela Christiano, PhD: Major advancements in the molecular understanding of EB provide a pretty thorough understanding of the genes that are involved. Knowing a patient's specific mutations, we can reasonably predict the phenotypic expression, including a likely clinical course for an individual. What that level of understanding has allowed us to do is to shift the focus to repairing the skin of patients with the various forms of EB using advanced techniques, including cell-based therapies, gene correction technologies, and protein replacement therapies.

Dr. Ju: What advancements have been made with each of these approaches and how viable are they for potential clinical applications?

Dr. Christiano: As an example of gene therapy, a team at Stanford has made good progress using a transfused biovector that replaces type-VII collagen for patients with recessive dystrophic EB. They received a grant from the California Institute for Regenerative Medicine that facilitated the ability to produce GMP-grade retrovirus for clinical trials. A small phase 1 trial is underway that is showing promising results with respect to safety, gene replacement, expression of corrected protein, and improved wound healing.

In the protein therapy realm, Drs. David Woodley and Mei Chen at USC have developed a way to manufacture recombinant type-VII collagen. They have shown proof-of-concept benefit with this protein in a mouse model of recessive dystrophic EB. The work formed the basis for the company Lotus Tissue Repair that they co-founded, and Lotus was later purchased by Shire.

Within cell-based therapies, allogeneic bone marrow transplant, as well as the use of exogenous fibroblasts, have both been promising. Allogeneic bone marrow transplants have been performed in patients with recessive dystrophic EB (using complete myeloablation) at the University of Minnesota, which has shown some clinical benefit. Because of the significant side effects associated with complete conditioning, there is an ongoing exploration of reduced intensity conditioning for partial ablation for EB patients, first performed at Columbia University.

Dr. Ju: You are involved in research in this area, as well. Can you share some information about the approach you are looking at?

Dr. Christiano: We are very fortunate to be collaborating with the Stanford lab and Dennis Roop's lab at the University of Colorado on a concept that relies on CRISPR/cas gene editing used in conjunction with induced pluripotent stem cells (iPSCs). The goal would be to use CRISPR to correct the specific mutation in a patient's pluripotent stem cells—which are iPSCs cultured outside the body—and then to take those corrected cells and differentiate them into the various skin cell types, such as keratinocytes, fibroblasts, melanocytes, and others. These bioengineered cells could be used to make 3D skin grafts that could then be grafted back onto the patient. We have already demonstrated proof-of-concept of this gene editing technique in the lab with cells from patients with dominant dystrophic EB, and were able to produce iPSCs that could be differentiated into keratinocytes and fibroblasts making corrected type-VII collagen. We are refining the approach to address other forms of the disease as well.

With the IPS work, the biggest concern is safety. With CRISPR, when you target a given mutated gene, how specific is the enzymatic cleavage? Are you getting off-target mutagenesis? There is a lot still to be learned about the technologies as they move toward the clinic, with safety as the foremost consideration.

A variation of this approach is to take advantage of a phenomenon known as revertant mosaicism. Here, the correction of genetic mutation occurs in patients by virtue of a natural and spontaneous gene correction event that occurs in a small number of keratinocytes. In areas of skin where revertant mosaicism has taken place, individuals affected by EB typically have patches of healthy, unaffected skin. It may be possible to use keratinoctyes from those spontaneously corrected sites to generate the induced pluripotent stem cells, as our group recently demonstrated, in addition to making genetic corrections through CRISPR.

Dr. Ju: As you survey the current landscape of EB, how do you envision treatment being different in the next 5 to 10 years?

Dr. Christiano: I think it will be very different. Something that makes EB an especially good target is that it is not necessary to achieve 100% gene restoration to get good clinical efficacy. We know from genetic studies that carriers of EB mutations, who do not have clinical manifestations, typically have about 50% normal levels of type-VII collagen, whereas patients with milder dominant dystrophic EB have about 12% and those with severe recessive dystrophic EB have essentially zero type-VII collagen. Thus, the therapeutic window is very favorable: even a small a change from zero to 12% levels of type-VII collagen could have a profound difference in clinical outcome.

Another point is that when patients with EB are currently treated with a skin graft, they are given a simple skin construct consisting of a dermis and epidermis without nerves, vascular channels, or hair follicles. When these constructs are made commercially, they are allogeneic, so they provide only temporary coverage of a wound, and are eventually lost. In the era of precision medicine, we are hopeful that one day we may be able to engineer 3D skin constructs using a patient's own cells that actually contain appendages, such as hair follicles, that contain channels that nerves can grow through, that contain Merkel cells that can actually transduce touch, and that even have melanocytes to produce pigment. Five years may be a bit overly optimistic, but I am confident we can make tremendous strides in the coming decade. ■

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