Nature Reviews Genetics | AOP, published online 15 May 2012; doi:10.1038/nrg3252

AN INTERVIEW WITH...

Elaine Fuchs

The 2012 March of Dimes Prize in Developmental Biology has been jointly awarded to Elaine Fuchs, of the Rockefeller University and Howard Hughes Medical Institute, and to Howard Green, of Harvard Medical School, for their pioneering research on the molecular workings of skin stem cells and inherited skin disorders. The prize recognizes researchers whose work has contributed to our understanding of the science that underlies birth defects. We talked to the winners about their achievements and the impact these have had on human health. This month's interview is with Elaine Fuchs, who spoke to Hannah Stower. The interview with Howard Green will appear in our July issue.

How did you come to focus on skin?

Originally, I was trained as a chemist, then a biochemist. Having worked on bacterial sporulation for my Ph.D., I wanted to do something more medically orientated. As a biochemist, I felt human cell culture might be a good model system. I thought, if I want to study how cells malfunction in human disease, then I need to begin by studying how normal cells function. At the time, human epidermal cells could be maintained and propagated *in vitro* over hundreds of generations without losing their ability to generate epidermal tissue. I was fascinated by the system; it seemed perfect for studying growth and differentiation. Back in those days, we didn't call them stem cells, we called them epidermal keratinocytes. They were the first stem cells that were ever cultured and propagated *in vitro*.

From what I understand, at this time you pioneered reverse genetics?

When I began as an Assistant Professor at the University of Chicago, I was driven by studying the basic biology of skin stem cells. This ultimately led my group to the genetic basis of different human disorders, particularly those of the skin. At the time, human geneticists were choosing their disease — cystic fibrosis, muscular dystrophy, and so on — and then they used a technique known as positional cloning to slog their way through the megabases of DNA to find the gene mutation at the root of the disorder. But typically, positional cloning offered no clues to what I felt was the most interesting facet of studying a human genetic disease, namely how a defective protein causes disease. Might it be possible to use a reverse approach — start with a protein and work your way up to a disease? If nothing else, we would have fun taking this strategy!

Keratins were the major structural proteins produced by normal epidermal cells. We determined their sequences, and studied how they form an extensive network of filaments within the epidermal cell. We got to the point where we could engineer individual amino acid mutations in a conserved region of a keratin, and when we introduced the mutant protein into our cultured epidermal cells, it completely perturbed their mechanical framework. This was wonderful but what did it mean for human disease? We thought maybe a mouse expressing a mutant epidermal keratin might provide an answer. Transgenic mouse technology had just been developed, and my student went off site to one of the few labs that could teach us. Upon returning to my lab, my student made mice expressing a mutant version of a keratin gene expressed by the proliferative cells of the epidermis. The mice got bad blisters after walking around the cage. The pathology showed that the blistering was caused by a mechanical stress-induced rupturing of the proliferative epidermal layer.

Our next step was to buy a dermatology textbook. We came to the page on epidermolysis bullosa simplex (EBS) — point-for-point, it had all of the features characteristic of the particular blistering phenotype of our mice. Within 6 months, we had teamed with dermatologists, obtained skin biopsies from patient volunteers and elucidated the genetic basis of human EBS. This was the first human genetic disorder solved by my lab, and we had taken the exact opposite approach that was being used at the time. What were the advantages of this strategy? We already knew that keratins are differentially expressed as pairs by virtually all epithelial cells at different stages of growth and differentiation. Hence, it was then just a matter of time to elucidate the genetic bases of many additional keratin and other intermediate filament disorders that fit the paradigm of EBS.

So what has kept your research focused on skin?

It's constantly asking new questions and then developing whatever technologies are necessary to address them. Our current questions centre on how the stem cells of our body work. These special cells must mobilize into action to rejuvenate tissue or repair a wound, but then return to rest once their job is done. We've been exploring these signals that turn stem cells on and off and have a pretty good molecular understanding of the process. We're also interested in how stem cells can last an entire lifetime. Just recently we had a paper that deals with this subject. We stick with skin, but we keep digging deeper.

What do you think the future holds for regenerative medicine?

Culturing epidermal cells has been used for years to treat burn patients. More recently, these methods have been adapted to culture stem cells to treat corneal blindness from industrial accidents. As long as there is one good eye to serve as a source of stem cells, the blind eye can be completely cured. But what happens when both eyes are blind and there are no corneal stem cells to graft? Might we be able in the future to convert a skin stem cell into a corneal stem cell, and hence treat total blindness with stem cells from the skin?

Other breakthroughs are happening in identifying the stem cells within cancers. Within this past year, we have identified the cancer stem cells from squamous cell carcinomas, one of the most prevalent and life-threatening of human cancers. Surprisingly, hundreds of differences distinguish cancer stem cells from their normal counterparts. We're now trying to figure out which differences are most important and whether some of these differences might be useful in improving diagnostics and treatments of these cancers. With the tremendous technological advancements in hand, the field is moving at a dizzying pace!