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How Does the Skin Repair Itself? A Study on Skin Regeneration

Dr. Greenberg:
Welcome to *DermConsult* on ReachMD. I'm Dr. Michael Greenberg and joining me today to discuss a recent study that's giving us new understanding of how the skin repairs itself is Dr. Svitlana Kurinna, who's a research fellow in the Division of Cell Matrix Biology and Regenerative Medicine at the University of Manchester. Svitlana, thanks for being here, today, especially coming from across the pond.

Dr. Kurinna:
It's great to be with you, as well.

Dr. Greenberg:
So, to start us off, Svitlana, can you tell us about your background and how you became interested in skin regeneration?

Dr. Kurinna:
I started off learning the mechanisms of cell growth in proliferation, first in myeloid leukemia and actually on your side of the pond at MD Anderson Cancer Center in Texas. Because bone marrow we know that it provides a really a lifelong supply of cells that circulate in our blood and this is why bone marrow is so prone to oncogenesis. It was a great model to engage in studying these mechanisms of repair when I first started off. And so, later I continued into my Ph.D. studies on liver regeneration, as a model again of tissue repair and then in the post-doctoral training done in Zurich at the Swiss Institute of Technology, I continued on to skin regeneration.

Dr. Greenberg:
So, listen, without going into too much detail, how does the skin regenerate itself normally?

Dr. Kurinna:
Yes, I would probably like to remind first about structure of the skin for those who are not dermatologists. But I also maybe saying something new to the dermatologists, as well, from the perspective of a cell biologist.

So there are two major parts of the skin, the epidermis and dermis. The epidermis consists of several layers particularly in humans it's thicker and has suprabasal layers and the basal layers where these so-called transient amplifying cells hide. And they're really the progeny of the stem cell that we've been trying to hunt for many years in the human skin and it's very difficult to put your finger on their identity. But it is mainly these transient amplifying cells over the basal layer of the epidermis. So, something that is facing dermis in the suprabasal layer of the epidermis that is responsible for regeneration, as far as we know. And so, there is a cross-talk between these epidermal and dermal niches that is absolutely essential for the regeneration and the homeostasis of the skin and also to support these elusive stem cells that are probably hiding somewhere in the hair follicles and in between but we don't really know for the human skin.

Dr. Greenberg:
OK. So, you've been working with transcription factors. Tell me about them and how they influence skin repair.

Dr. Kurinna:
I am coming from studying the oncogenic transcription factor p53that was in the graduate school in Texas where I learned that this transcription factor and its entire family that includes now the skin-specific member p63, they sit on the DNA all the time but also very dynamically regulating the expression of the genes. And this is what I really was interested to understand when I was in the lab of Shelley Barton so my Ph.D. supervisor who taught me how to unwind these mechanisms of the interaction between different transcription factors in the DNA. So later in Zurich at the the Swiss Institute of Technology, Serbina Verdener, my post-doctoral supervisor, drew my attention to another essential transcription factor in the skin called Nrf2. And this transcription factor is responsible for protection of the skin from the oxidative stress.

So, in my own work, I combined these two transcription factors the studies to see if really both of them are important in regeneration of the skin because the p53 family member p63 engages proliferation of the skin during its growth and development but as Nrf2's major function is to protect the skin from the oxidative stress and to possibly also augment its growth and this is the new finding that has been going on in the field of dedicated to the Nrf2 research.

Dr. Greenberg:
So, these factors actually augment healing in the skin?

Dr. Kurinna:
Yes. This is what we think, that they're essential and if activated transiently and under certain conditions and certain cells, we really think that they can augment it. I'm just trying to be careful here because there is a plethora of Nrf2 activators that have been used in all sorts of supplements on the market that we don't really know how they work at the molecular level. So, I'm trying to be very careful and precise here to say that we think that the activation of Nrf2 and p63 together can enhance proliferation of keratinocytes because as this is what we see in vitro. But we only discovered one specific mechanism for this it's through this cyclin-dependent kinase 12. And we believe that it is the early induction of differentiation that has to come in play, here. So it is a little bit more complicated than I would like it to be but yes, the short answer is we are after augmenting the proliferation and regeneration of the skin.

Dr. Greenberg:
So, can you help us also by further explaining the significance of suprabasal keratinocytes and why they're significant to your research?

Dr. Kurinna:
So, we know that there are many suprabasal cells in regenerating human epidermis that could be engaged in the process. But we lack the models to study this mechanisms. So, the available models do not reflect the complexity of the basal and suprabasal subpopulations of keratinocytes. For example, in one sequencing experiment, that involved single cells isolated and sequenced, the computer classed over twenty-five different subpopulations of keratinocytes. If you can imagine most of these we cannot tell apart when we look at the at the biopsy and the histology of the skin. So there are so-called positioning factors, the proteins that define a temporary gene-expression patterns in human epidermis, and they will define the subpopulations of what I would like to think really transient epidermal stem cells. And so following the injury, this epidermal stem cells could express, cell surface markers that we previously didn't know or thought they were belonging to other groups of cells and all of this is happening with certain velocity because the mRNA is also being regulated, just as the DNA is regulated, the RNA is also being very actively engaged in this and being regulated through other additional factors, so all in this together, makes this fluid state of stem cells difficult to catch. So, in my lab, we are currently establishing the 3D models of human skin where we can target the expression of these fluid genes in mRNAs using microRNAs and so in this way, we can test the contribution of each individual and neuroregulators of transcription and translation in the repair of the epidermis.

Dr. Greenberg:
For those of you just tuning in, you're listening to *DermConsult* on ReachMD. I'm Dr. Michael Greenberg, and today I'm speaking with Dr. Svitlana Kurinna about her, her study on how the skin repairs itself. So, let's go on, Svitlana. If we look beyond the skin for a moment, how do you see this research influencing regeneration of other tissues and organs?

Dr. Kurinna:
Similar molecular mechanisms drive repair of other organs, not only the skin. The difference is usually in the master regulators, so these transcription factors that dynamically sit and regulate the DNA in the expression of the genes. Plus, the fine-tuning microRNAs that would regulate mRNAs. Then there are different niche factors that also, of course, contribute to individual organ regeneration. But the principal mechanisms behind all of these processes seem to be quite conserved, and I would say there are few when you look at the molecular pathways on a big poster, they may look overwhelming but the ones that are activated at the given time, in the given cell, aren't that many. So, I think that our finding and my own transition in my career from studying one regenerating organ to another illustrates the point that we can take these mechanisms beyond one organ and apply the principal.

Dr. Greenberg:
Great. So, now let's take a step into future fantasy land, for a second, OK? So, in dermatology, do you see any way that your research can help avoid scars or minimize scars after surgical removals?

Dr. Kurinna:
Yes, indeed, this is a dream land that we would like to talk about. We had a similar discussion with a colleague of mine recently and he was arguing that in the adult body, scars, from deep wounds are unavoidable. There is, there is really no way to not have scars, at all. And so from available research models the embryonic tissues are known to heal without scars. But because the skin of the adult body is facing the air and the rest of the environment, the priority is to close the gap in a wound to prevent infection of water loss, etc. rather than to restore the organ as an intact organ, as it was. So, I think that it is still possible, but we really need first of all, to understand how this

epidermal compartment regenerates in a tissue culture model and maybe reproduce it in the tissue culture model to such extent that we can just transplant it back. Because I really don't see how in in a problematic wound on in situ, so on-site, we can manipulate all these factors. So, I say that yes, this is an achievable dream if we know what is really happening in the wound bed and particularly in the neo-epidermis.

Dr. Greenberg:
Well, I hope you carry on with that because remember, there used to be a dream that one day we get to the moon and people laughed at that and guess what? We've been there.

So, what's next in your thinking about skin regeneration? What are you going to focus on next in your research?

Dr. Kurinna:
In my ideal world, we can grow as much skin in vitro as we need to cover large area of wounds and, by doing so, to help people with ulcers. I would like to see it done in a less research-intense, complicated setting, but for now, we need to keep it complicated because of individual differences between the cases and the studies.

Dr. Greenberg:
So, finally, last question, can you talk about growth factors and the advantage of your compounds over-growth factors?

Dr. Kurinna:
Last time when I spoke to a patient who came for an appointment to restore a tendon in the kneeI specifically asked this person if there is anything that, other than the growth factors, that she has seen in her prescriptions and I was taken aback by her response that no, nothing really works, only growth factors work. So this really gave me a kick. I thought, 'OK. It's about time I really try different compounds and see, in the lab, and see if they really make keratinocytes grow better without causing major defects'. Now, I'm sure these studies are going on in many other labs across the world, but it's the implementation that we really need to enhance somehow it's been always difficult to for a researcher to be bold enough to say, 'OK. I've discovered this mechanism, this compound is really inexpensive let's give it a try'.

Dr. Greenberg:
Thank you. Well, that's a great way to round out our discussion focusing on your great and interesting research on skin regeneration. And I wanna thank you Svitlana for being on this program. It was great speaking with you, today.

Dr. Kurinna:
Thank you very much.

Dr. Greenberg:
For ReachMD, I'm Dr. Michael Greenberg. To access this episode and others from our series, visit ReachMD.com/DermConsult, where you can be part of the knowledge. And we thank you for listening.