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Do shoot the messenger: taking aim at RNA to treat genetic skin disorders

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Abstract:

It might be possible to treat genetic skin diseases by correcting defective RNA. In this issue of Experimental Dermatology, Bornert et al review the latest developments in this area. Progress is rapid and impressive. Clinical use of RNA correction looks set to soon become reality. The future looks bright indeed. But, as always, we have to think before we act. In my comment, I provide a much-needed reality check.

For the vast majority of genetic skin disorders there is no specific treatment. Our understanding of their biology, mildly put, is still limited. As a result, small molecule approaches are not a viable option right now. There are a few notable exceptions, such as tuberous sclerosis (1).

However, the gene defects underlying most genodermatoses are now known. One could therefore consider dispensing with all that complicated biology. Instead, one might attempt to correct or replace the faulty gene, or supply its product. Unfortunately, most such approaches don't work. For genetic skin disorders, they haven't even been tried. Some groups have tried to treat recessive dystrophic epidermolysis bullosa (RDEB) with allogeneic bone marrow transplantation or mesenchymal stem cells (2). Transient symptom relief was reported with both modalities. Yet, there is no convincing proof of efficacy beyond a placebo effect as it is not possible right now to objectively measure how severe RDEB is. Also, allogeneic bone marrow transplantation is a risky procedure.

Much work has been done on cell therapy. Here, the genetic defect is corrected in isolated patient keratinocytes that are then transplanted back onto affected skin. This approach has

yet to prove its merits in the clinic. Moreover, gene correction in most work published to date was achieved with retro- or lentiviruses. There are still significant safety issues surrounding the use of such viruses (3). CRISPR/Cas9 mediated gene editing is a recent development and holds great promise (4), but will take a long time to become useful as a therapy because of practical and ethical concerns. So it seems that our patients are still facing a bleak future.

But there is hope. Treatment of genetic skin disorders could focus on (pre-)mRNA. Avoiding permanent alterations to the DNA – even when limited to stem cells – circumvents many ethical issues. One would also not have to deal with difficulties inherent in cell or protein replacement.

Recent advances bring RNA-based therapies for genodermatoses closer to the clinic, but several challenges remain. As Bornert et al discuss in this issue of Experimental Dermatology (5), there are several ways to target (pre-)mRNA for therapeutic benefit. Antisense oligonucleotides (AON) or small interfering RNAs (siRNA) can reduce gene expression. siRNA has been tested with some success, in a patient with pachyonychia congenita (6).

However, gene silencing has important disadvantages. The knockdown approach applies to dominant disorders only. Also, it is mutation-specific although in some cases one could target SNPs that are in phase with the mutation. That would make knockdown applicable to more patients, as long as they have the right SNP.

Trans-splicing is a more exotic technique that is not mutation-specific (5). Here, a wild-type piece of RNA replaces the part of the endogenous pre-mRNA that contains the mutation. Finally, AON can modulate splicing so they could cause exons with a disease-causing

mutation to be skipped. This results in expression of a shorter protein. In some cases, enough functionality remains to treat the disease. This approach is being pursued for recessive dystrophic epidermolysis bullosa (7).

Of course, all these methods need delivery of oligonucleotides to the target tissue. Upon systemic administration, these molecules accumulate in liver and kidney, not the skin (8). Tinkering with the backbone chemistry might help to achieve dermal delivery, but for many genodermatoses the epidermis must be targeted. So topical application seems to be the most appropriate approach. Since oligonucleotides are large molecules, that is going to be a tough challenge. Several methods to overcome this obstacle have been proposed and tried (9), so far without much success. A major effort in this area is necessary, if RNA-based treatments for genodermatoses are to work.

Other obstacles remain and Bornert and colleagues discuss these, except for one that I already mentioned in the context of RDEB treatment. We need objective outcome measures for future clinical trials in genetic skin disease. This need is all the more pressing for rare disorders, where the number of patients to be treated will be low. Unfortunately, genodermatology does not seem to be in a hurry to develop outcome measures. This must change to make sure that people with a genetic skin disease can profit from the recent, dramatic advances in biology. Patient organisations, scientists and caregivers should therefore make developing objective outcome measures their number one priority.

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