Scientists 'switch off' defective genes in cure for skin blistering diseases

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(Medical Xpress) -- Scientists have taken major steps forward to curing severe skin blistering diseases like epidermolysis bullosa which ruin thousands of lives in the UK every year.

The team at Newcastle University have been focusing on a form of gene therapy to 'deactivate' defective proteins that cause the skin to blister.

The team of scientists in the Institute of Cellular Medicine, headed by Dr. Julia Reichelt, have successfully proven that their technique based on zinc-finger nucleases (ZFN), can now be applied to the actual defective blister-causing proteins themselves. Thus far, they have focused their efforts on isolated skin stem cells which have been engineered to be fluorescent green, a more cost effective and quicker way to prove that such a method could work. The study has been published in the journal *Stem Cell Rev and Rep*.

Applying the same ZFN technique to the green fluorescent proteins from skin stem cells as they would with defective skin blistering proteins, Dr Reichelt and her team were able to successfully switch off the green fluorescence in one in every five of the treated cells - a process the team now intend to apply to the actual defective proteins.

Being able to switch off these harmful proteins that cause the skin to blister could prove to be the vital breakthrough which may lead to a cure for extreme diseases like epidermolysis bullosa (EB), where the very slightest of contact with the skin can cause it to blister. The disease

recently drew attention to itself in the BBC programme Stormchaser: The Butterfly and the Tornado and back in the 2004 documentary The Boy Whose Skin Fell Off. Although conditions like EB are rare, estimated to affect one in every 17,000 children born in the UK, there are currently about 5,000 people living with it in the UK.

It's an exciting time for the researchers, though they are keen to point out that this result is only the first step in a long process. Dr Reichelt says: "We are still in the very early stages of being able to develop an actual form of therapy. The idea is to isolate skin stem cells from the patients, then to treat these skin stem cells with specific ZFN in cell culture in order to switch off the disease-causing gene. Once this happens, those treated cells would then be transplanted back to the patient's skin, though we still have to establish the transplantation method best suited for this, as we have to make sure the treated cells take properly and remain active for a life time. In cell culture experiments thus far, we showed that even after treatment with high ZFN doses, skin stem cells retained their full potential to regenerate skin."

The same ZFN technology can be used for other blistering skin diseases such as epidermolytic ichthyosis, as ZFN can be engineered to specifically recognise the disease-causing gene. Dr Reichelt adds: "We, and other researchers in the field, are very enthusiastic about the usefulness of ZFN technology for gene therapies, particularly for gene therapies using stem cells. My ultimate aim is to help develop a permanent treatment for blistering skin diseases in patients."

Matthew Patey, Chief Executive of the British Skin Foundation which funded the project says: "Skin diseases like EB can devastate lives, so hopefully the research team's work will mean a cure can be found for people who live such conditions in the not too distant future. As with all research, it takes time and money to make it work, so it's important that

as a charity we are able to continue to fund such pioneering work like what Dr Reichelt and her colleagues are doing at the moment."

More information: Highly Efficient Zinc-Finger Nuclease-Mediated Disruption of an eGFP Transgene in Keratinocyte Stem Cells without Impairment of Stem Cell Properties. Höher T, et al. *Stem Cell Rev*. 2011 Aug 27. Epub ahead of print DOI:10.1007/s12015-011-9313-z

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