CHIEF SCIENTIST OFFICE

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RESEARCH PROJECT BRIEFING



Molecular Characterisation of Atopic Dermatitis

AIMS

- Atopic dermatitis, also known as eczema, is the commonest inflammatory skin disease in the Western world affecting roughly 20% of children and 10% of adults. An inflammatory skin disease is one in which there is redness and irritation of the skin however in eczema there is also itch and dryness.

- To find out what is different in the cells and chemicals in the skin of people with short-term eczema as compared to those with long-standing eczema so that in the future treatments may be developed which target chemicals which are specifically increased in those with short-term as opposed to long-standing eczema. The cells contain special instructions for our bodies to grow and function and these are called genes. I wish to study which genes are giving most instructions in the short-term versus long-standing eczema.

- One key chemical which I wish to focus on is prostaglandin E2 which is produced in many cells including immune cells. It was shown to be important in contributing to thickening and redness of the skin in mice. I wish to understand whether it is also important in causing changes in the skin in eczema patients.

KEY FINDINGS

- The genes giving most instructions to the cells within the skin were different in short-term as opposed to long-standing eczema
- The gene giving instructions for Prostaglandin E2 to be produced was increased in the long-standing eczema patients compared with the short-term eczema patients and it may be important to try to control this chemical in the long-standing eczema patients in the future by developing medications to block some of its effects to help reduce the skin changes in these patients

WHAT DID THE STUDY INVOLVE?

This study involved taking skin samples from those with short-term and those with long-standing eczema patients and comparing these with the healthy controls. One half of each of the skin samples was sent to a laboratory where the genes/instructions from the skin of each person involved was read by a machine to see which were most important for that person i.e. to determine whether there were increased amounts of instructions or reduced amounts of instructions from a particular gene. I took the other half portion of the skin sample and “stained” it. This means adding a colour or dye to study the skin. This reason for this is explained as follows: the effects of the specific genes/instructions is the production of building blocks in the skin which can be coloured and visualised using special chemicals which produce a colour to see if the instructions have actually been followed in the skin resulting in changes in the skin. I added one of these special chemicals which is specific for one type of building block to see if there was any difference between patients.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

- In eczema patients, there were greater amounts of genes/instructions to direct our skin to make more cells as well as increasing the instructions to promote the production of the thickened outer layer of skin that we can see with our eyes when we look at our skin. This layer acts as a barrier

preventing the much-needed water from escaping and the bugs and dust etc. from getting into our bodies through the skin.

- The key finding was that patients with short term eczema had less of the genes/instructions to build or remodel key scaffolding structures which give the skin its structure as compared with those with longer term eczema. These scaffolding structures are very important as they also can influence how cells which defend us act so can support more entry of these immune/defence cells into the skin or potentially influence what role these defence cells play. I coloured the skin samples to see if the increased instructions led to increased production of the building blocks specific for that gene in the long-term patients. This showed increased amounts of the building blocks for one fo the specific scaffolding genes.

- The instructions for the manufacture of prostaglandin E2 were increased in a subgroup of long-term eczema patients as shown by increased amounts of these specific prostaglandin E2 genes detected compared with all of the other participants and patients.

WHAT IMPACT COULD THE FINDINGS HAVE?

Patients:

The genes which we found were giving more instructions to the skin in eczema patients compared with normal skin could be studied in more detail to understand if these could be measured in the future to predict who might be more at risk of longer-term eczema for example. Also, future studies might consider assessing whether these “instructors” could be manipulated using medications to reduce the redness itch and dryness of our patients’ skin.

Policy:

Current management of eczema involves following NICE (National Institute of Clinical Excellence) guidelines which do not differentiate between subgroups of eczema patients and suggests a “one size fits all” approach despite the fact that we know eczema is different for every patient. This PhD has contributed to the need for improved understanding of differences between eczema patients according the amount of a given type of instructions/genes in their skin and may stimulate a renewed

focus on adapting treatment approaches to suit an individual patient according to these excessive or reduced instructions in order to ensure that we get it right the first time instead of forcing treatment pathways on patients without due consideration of what the patient may benefit from most at the very outset.

Practice:

This PhD allows us to begin paving the way for a more patient-focused approach to treating eczema with each individual treated as unique with their own treatment needs to restore normal levels of these instructions and so improve their skin disease.

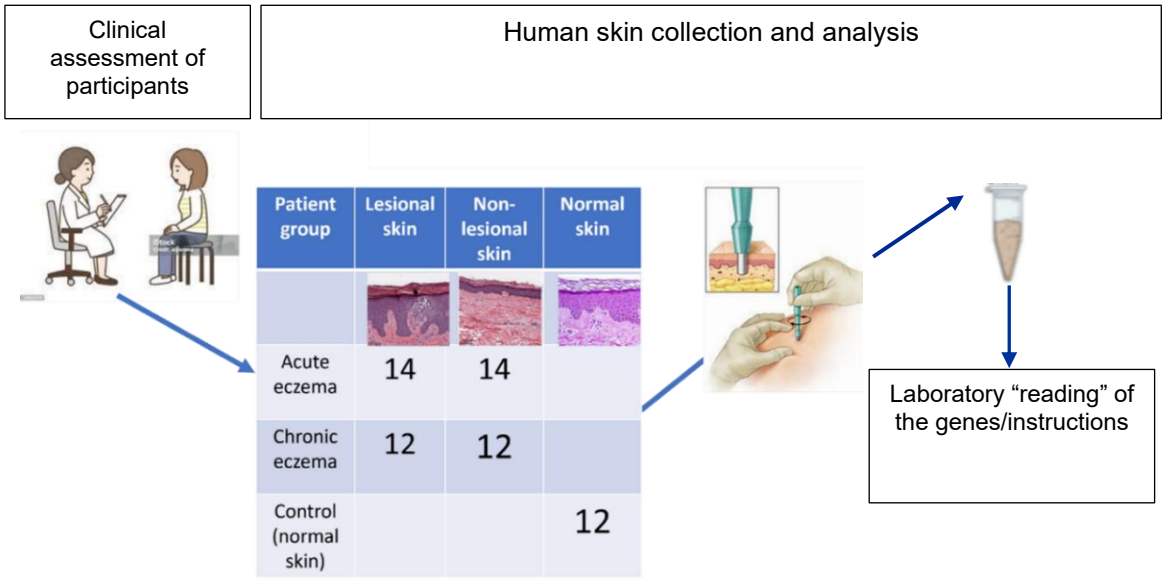

Figure 1: Schematic overview from participant recruitment through to tissue collection, "reading" the genes/instructions and then the analysis of the information gained from this "reading". (created with Biorender.com)

Figure 1 demonstrates the type of patients which were recruited to the study. The acute eczema patients refers to those who had short term eczema while the chronic eczema patients refers to those with longer term eczema.

Non-lesional samples are samples taken from eczema patients which appear normal but have different amounts of "instructions" compared with healthy skin. Lesional skin is skin which looks red in the short term patients and is thick in the longer term patients. There were in total 14 short term and 12 long term eczema patients with 28 and 24 samples being taken from each of these

two patient groups respectively (2 samples from each patient i.e. lesional and non-lesional) and 12 healthy control participants (1 sample only was taken from the healthy patients).

Control skin was from healthy patients who do not have eczema so that we could have a means by which to compare our eczema patient skin to understand which "instructions" were changing in eczema. Samples were taken from the patients and healthy controls and sent to a laboratory for the cells "instructions" be "read". The information read by the laboratory was then analysed and results were disseminated in the thesis.

HOW WILL THE OUTCOMES BE DISSEMINATED?

A manuscript is underway in order to disseminate the outcomes. Already I presented this data (oral and poster presentations) at numerous meetings including the British Society for Immunology, SIGNET meetings, British Society for Investigative Dermatology, Scottish Skin Biology club meetings (shortlisted for the pre-doctoral award), 9th European Workshop on Lipid Mediators (awarded Young Scientist award), Young Lipid Scientist Award (Society of Chemical Industry) presentation (shortlisted by the Society of Chemical Industry), University of Edinburgh Research in Progress meetings among others. I will approach the Eczema Outreach Society to ensure I discuss the findings with the patients and involve them in moving forward by obtaining their thoughts and ideas about the outcomes. I will also approach the Edinburgh Fringe Festival to ensure these outcomes are reaching the public in general to expand on public understanding about eczema and my eczema research outcomes as well as involving the public in the future of my research. I wish to seek a CSO fellowship grant to allow me to continue my research focused on moving forward with investigating the differences between eczema patients in more detail using these outcomes as a foundation and basis.

CONCLUSION

This research study set out to try to help us understand why some people with eczema have acute /short-term flare ups but other people develop long-term disease. We did this by studying the differences in the "instructions" provided to the body by genes in different eczema patients.

We found that the activity of genes controlling the skin barrier and the genes controlling the number of skin and immune/defence cells produced in the skin was increased in all eczema patients. However, some of the long-term eczema patients had increased amounts of instructions to increase immune/defence activity as well as structural activity to physically support the skin's structure. Instructions to increase the amount of the chemical called prostaglandin E2 (PGE_2) were detected in the long-term eczema patients compared with the short-term eczema patients.

In summary, we have shown that acute and chronic AD patients have differences in the activity of specific types of genes including those involved in the immune system and those involved in the skin structure. Within the group of long-term eczema patients, there were also differences between patients with increased instructions to produce more prostaglandin E2 which causes ongoing inflammation (redness and skin changes due to the long-term exaggerated response of the immune system). Treating this subgroup of chronic patients in the future may involve trying to create medicines which counteract prostaglandin E2 thereby preventing longer-term inflammation.

RESEARCH TEAM & CONTACT

Fiona Cunningham

Chengcan Yao

Richard Weller

Adriano Rossi

Institute for Regeneration and Repair,
University of Edinburgh

fiona.cunningham@ed.ac.uk