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# Epithelia and innate immune cells communicate to initiate sterile inflammation

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**Work done in the lab of Prof. Srikala Raghavan at Institute for Stem Cell Science and Regenerative Medicine (inStem, Bangalore).**

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Uttkarsh Ayyangar is a graduate student (DBT-SRF) in the Raghavan Lab. He has been done his bachelors (B.Tech Biotechnology) from SRM University Chennai where he was the first rank holder. He is also recipient of prestigious Khorana Fellowship (2016). Apart from science, he enjoys Indian classical music and badminton.

**How would you explain your research outcomes to the non-scientific community?**

Skin is the largest and the outermost organ of the body that acts as a barrier to external agents. It comprises of an outer epidermis and inner dermis which are separated by a meshwork of proteins and carbohydrates known as the basement membrane (also called the extracellular matrix). To serve the protective functions of the skin, both the epidermis and the dermis harbor different types of immune cells (white blood cells) that protect us from infectious microbes and also aid in repair function upon injury. Broadly, these immune cells are classified as innate and adaptive immune cells. The innate immune cells form the first line of defense that fight infections and activate the adaptive immune cells, the second line of defense, which further promotes clearance of infection.

During tissue damage, increase in the recruitment of immune cells is followed by pain, redness, swelling, and heat in the damaged tissues, a condition termed as inflammation. When this inflammation occurs in the absence of infection, it is considered sterile. While a bulk of research highlights the role of immune cells in different stages of inflammation; the initial events that set up the inflammation are less understood. Macrophages, a type of innate immune cell, are a group of specialized immune cells that can kill microorganisms invading the body as well as heal wounded tissues. They are among the first few immune cells to get recruited at the site of tissue damage and are capable of responding to diverse environmental factors.

In this study, we used a mouse embryonic model for sterile inflammation to unravel the contribution of different compartments of skin (epidermis, dermis, and macrophages) towards initiating a sterile inflammatory cascade. We showed that macrophages are the major immune cells present in the inflamed embryonic skin. They become active and express extracellular matrix remodelling enzymes leading to an exaggerated disorganization of the basement membrane. Consequently, removal of the macrophages reduced disruption of the basement membrane. We then asked what might be regulating this activation state of macrophages. We found that epidermis expresses a protein called cyclooxygenase-2 that causes the epidermis to express danger signals (cytokines and chemokines) that, in turn, influence the macrophages to become active and express basement membrane remodeling enzymes. This suggests that a crosstalk between the epithelia and the macrophage is an initial step in setting up an inflammatory condition in the skin. Taken together, our study provides clues to target the initial events in setting up inflammation and can be used to understand disease progression processes better.

**How do these findings contribute to your research area?**

Our findings have multiple implications. While much has been understood about the dynamics of the progression of inflammation in the later phases, much less is known about how inflammation is initiated. Our work suggests that in the most initial phases of development of inflammation, epidermis derived chemicals induce macrophages to produce enzymes that remodel the matrix. This crosstalk between epidermis and macrophages has not been shown previously and might have several implications in the field of skin therapy.
The treatment strategies currently being used to treat inflammatory skin disorders are biologics and immunosuppressive drugs which can have several side effects due to global suppression of immune cell activity. Hence, there is a need to develop newer strategies to treat skin disorders. Our work has identified specific pathways that initiate the inflammation process in the skin and therefore these pathways can be targeted for therapeutic intervention. The findings from this work can further be extrapolated to treat other chronic inflammatory disorders such as rheumatoid arthritis, multiple sclerosis and gout.
Secondly, recent studies suggested that cancer cells can recapitulate features of embryonic processes for their progression. Therefore, understanding macrophage characteristics in embryos can provide insights about the role macrophages in cancer development and progression.

**What was the exciting moment during your research?**

The most exciting moment for us was the time when we could delineate the contribution of epidermis, dermis, and macrophages by studying the up or downregulation in the expression of genes during sterile inflammation. This took us about 8 months to finish and results were certainly fruitful. The delineation helped us to understand how epidermis communicates with dermal macrophages to set up the inflammatory response in skin. Furthermore, the brainstorming sessions, the long healthy debates that we had with each other and our lab mates while building up the research work have always been thrilling.

**What do you hope to do next?**

We next aim to understand more carefully how the innate immune cells in the skin interact with other cell types in the skin such as T cells, fibroblasts and adipocytes in skin diseases such as psoriasis, atopic dermatitis. We also aim to analyze human skin to understand if the outcomes of our study in mice holds true in human skin. If so, we would be close to finding new therapeutic strategies to treat skin disorders.

**Where do you seek scientific inspiration?**

Oindrila: “Curiosity is the lust of the mind” is a quote by a seventeenth century philosopher Thomas Hobbes and I feel that explains best the source of my scientific inspiration. And if the curiosity fuels public good, nothing can be a better inspiration!

Uttkarsh: I derive inspiration from the work of amazing women in science who I have been extremely fortunate to work with. These include Drs. Sue

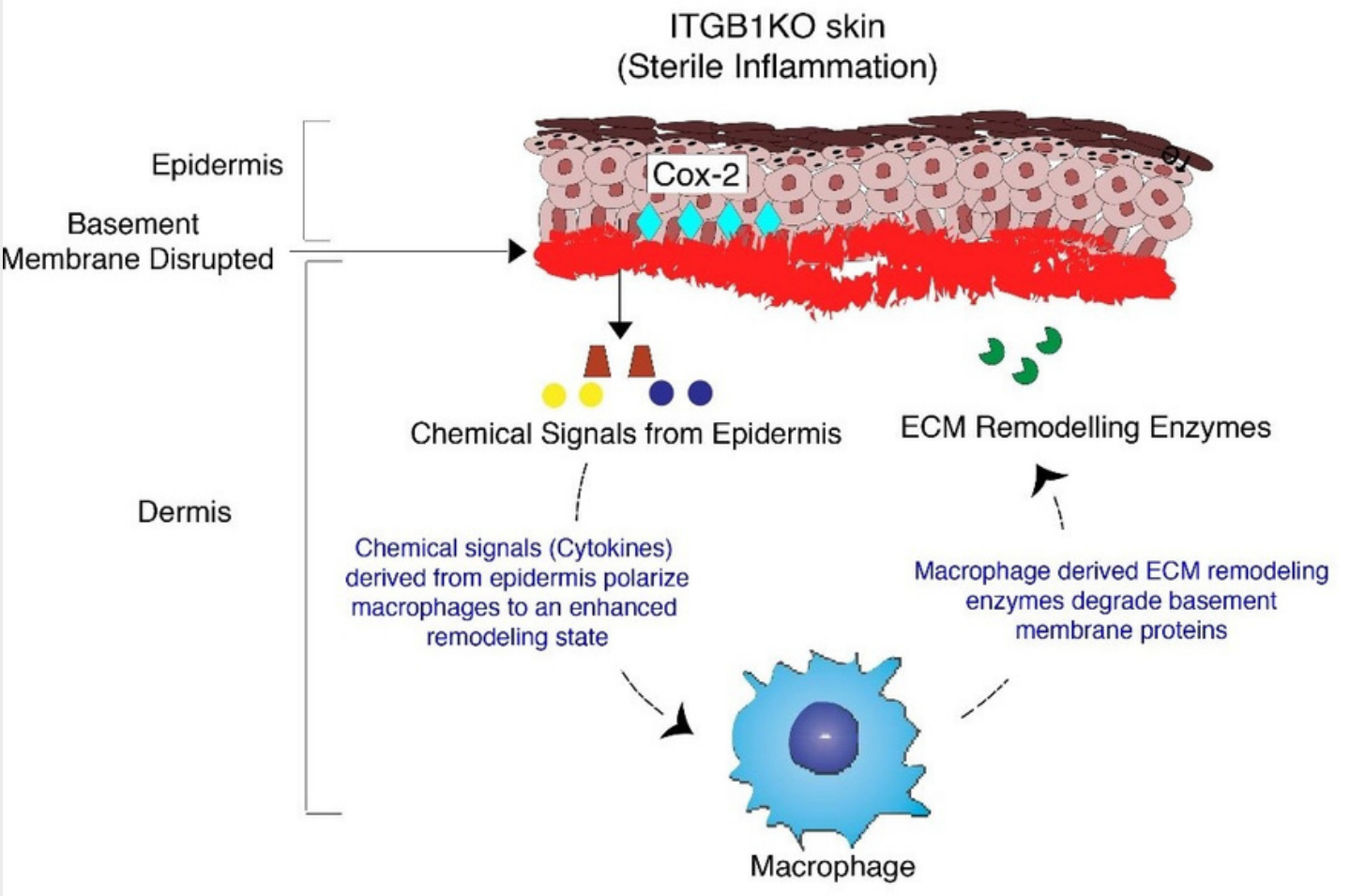
Crawford (BCM, Texas), Srikala Raghavan (A*STAR Skin Research Lab, Singapore and InStem), Ambika Kurbet (InStem, Bangalore), Mala Kanchana (SRM, Chennai), my colleague Oindrila Bhattacharjee and Ritusree Biswas (InStem) and my mother, Anila Ayyangar.

### How do you intend to help Indian science improve?

Over the years of experience as graduate students we realized that science communication is limited by the language barrier. We strongly feel that the love and appreciation for science can be propagated further by translating scientific articles into regional languages. We also feel that as experienced graduate students we should talk about both the success and failures that one faces while building up a research project so that aspiring scientists can not only take inspiration but also prepare themselves for the journey accordingly. This would make them more grounded, resilient and perseverant in their journey. Furthermore, we would propose to streamline the Ph.D. programs in India which in turn will go a long way in improving the research culture of the country.

### Reference

**Bhattacharjee O, Ayyangar U,** Kurbet AS, Lakshmanan V, Palakodeti D, Ginhoux F, Raghavan S. Epithelial-Macrophage Crosstalk Initiates Sterile Inflammation in Embryonic Skin. Front Immunol. 2021 Oct 14;12:718005.




The graphical abstract shows that the epidermis during the initial phases of sterile inflammation express chemicals such as cytokines that in-turn promote macrophages to express matrix remodelling enzymes. This interaction sets up the crosstalk between epithelia and the macrophages.