To begin, could you provide an insight into your previous work and describe how this led to an interest in the role of epidermal growth factor receptor in skin innate immunity?

Earlier in my career, I worked with different antimicrobial peptides (AMPs). I later found that many of the AMPs present in neutrophils that I had previously been working with are also expressed in the skin during wound healing and inflammation. I subsequently became interested in how the AMP expression was regulated in the skin. It was already known that proinflammatory cytokines induced the expression of AMP in the skin. However, more unusually, some of the AMPs I was looking at were clearly not induced in this way, despite the fact they were expressed in psoriasis – which is an inflammatory skin disease. Apart from inflammation, psoriasis is also characterised by hyperproliferation, so I began to study the effects on AMP expression by the growth factors that cause psoriatic hyperproliferation.

What exactly are AMPs and what makes them an important part of the innate immune system?

AMPs are the effector molecules that are responsible for killing the microbes. They are the body’s own antibiotic, so to speak. Neutrophils, that are cells specialised in killing microbes, contain numerous AMPs. They can be generated ‘on demand’ by release from storage granules or proteolytic cleavage from inactive proproteins; alternatively they can be synthesised de novo as they are in the skin. Knock-out studies demonstrate that AMPs are important for the host defence during infection. They also seem to have prominent effects in controlling inflammation, and are consequently sometimes referred to as ‘host defence peptides’.

How are AMPs able to prevent an array of bacteria-based viruses? What viruses fall under the Gram-positive and Gram-negative spectrum?

That is a good question. Although it is known that various bacteria are differently affected by AMPs, to date nobody has looked at the role of bacteria-based virus.

What are your views on the current therapies used to treat severe bacterial infections, particularly given the increase in antibiotic resistance?

We definitely need new antibiotics to combat the many bacteria which are now resistant to conventional therapy. Apart from this, the current use of antibiotic treatment must be changed. Too many people are prescribed antibiotics, and this promotes the development of resistance. Another problem is the insufficient treatment of chronic infections. Here again, there is often repeated antibiotic treatment which fails to clear the infection, but simply promotes resistance.

Could you discuss the methods or strategies you are employing to identify the benefits that are afforded by ‘wound licking’?

Wound licking is known to promote wound healing. As part of our research, we are stimulating whole skin and keratinocyte cultures with saliva. So far, we have found that this promotes an innate response, which is dependent on epidermal growth factor (EGF)-receptor activation. This may account for some of the benefits of wound licking and may also play a role for the symptoms found in xerotomia patients, who have a deficient production of saliva.

What results have already been obtained on the keratinocytes differentiation process, and what are your plans for future investigations in this area?

We have obtained some interesting new data regarding keratinocyte differentiation, which is important for the formation of a protective layer of the skin called the cornified envelope. Normal differentiated skin is rather efficient in keeping microbes at bay. We will be interested in looking at skin differentiation from a host defence perspective – in other words, we will look at skin differentiation as a host defence mechanism.

Ultimately, what impact do you expect this work to have in the long term?

Apart from the role of skin differentiation in host defence, disturbed skin differentiation is an important and largely unrecognised cause of inflammation. To date, we only have very limited knowledge of many aspects of the normal differentiation process. We do not even know about the major signalling pathways responsible for regulating epidermal differentiation. Thus, understanding how dysregulated differentiation causes inflammation will clearly open up the way for new, more specific and effective treatments of inflammatory skin diseases.
IT IS COMMONLY known that one of the skin’s primary functions is to act as a physical barrier against microorganisms. However, as the largest organ in the body, the skin has a much more complex and multifaceted role to play than a protective, passive barricade might suggest. The skin also actively produces antimicrobial peptides and proteins, which are vital in the defense against microbes after the infliction of wounds to the skin. More specifically, the skin generates growth factors that stimulate such regeneration. The growth factor response which is initially responsible for the regenerative process stops once the tissue has been rebuilt and the physical protective barrier is restored to its full function.

One cell-surface receptor which plays a vital role in the skin’s regenerative process is the epidermal growth factor (EGF) receptor. Other key agents in this process are antimicrobial peptides (AMPs), the effector molecules responsible for killing the microbes. The important function of AMPs hinges on their antimicrobial defence of the skin and other epithelial sites. While the scientific question as to how infection leads to the induction of the expression of AMPs in the skin is a well-worn research path, detailed studies into the role of EGF-receptor and AMPs have to date remained few and far between. Against this context, Dr Ole Sørensen is leading a project at Lund University focused upon unearthing the important role of growth factors in wound healing, and building understanding of the skin’s innate immunity more generally.

THE PROJECT

As part of its research, the Lund team has had the overarching goal of examining the expression of AMPs in human skin after it has suffered sterile wounding. Initially, they demonstrated that AMPs were induced through transactivation of the EGF-receptor. What was more unusual, however, was their finding that the antibacterial activity of the epidermis is actually increased by activation of the EGF-receptor. Additionally, the research established that the concentrations of AMPs in the epidermis of wounded skin exceeded the necessary amount, which could affect antimicrobial activity alone. Taken together, these results suggest the presence of a ‘defence mechanism’ in the epidermis, seemingly caused by wounding, that can prevent harmful colonisation of microbial material and related infection.

With this new knowledge in mind, Sørensen’s group has subsequently determined to establish whether sterile wounding induces the expression of AMPs in human skin.

In terms of meeting the key objectives of the project, the researchers have already found that the EGF-receptor is important for expression of AMPs and chemotactic cytokines. However, following their hypothesis that the EGF-receptor bears major importance for other skin innate immune defence mechanisms, as well as skin homeostasis and differentiation, the collaborators are determined to investigate and prove this as their long-term goal.

With regard to AMPs and the EGF-receptor in human skin wound healing, the project has highlighted numerous points of interest. During cutaneous wound healing, activation of the EGF-receptor plays not only a major role in the expression of the known AMPs in human skin, but also for the injury-induced production of chemotactic cytokines. These are the agents that attract leukocytes to the wound. Since activation of the EGF-receptor is shown to be important in wound healing, the innate immune response is therefore intrinsic to the normal wound healing process – even in the absence of microbes.

ACHIEVEMENTS AND CHALLENGES

To put the project’s achievements into perspective, 90 per cent of the cells in the human body comprise bacteria, yet despite the human body’s ability to generate specific and powerful responses to target invading microbes, the researchers have come to believe that normal body functions are adapted to the presence of microbes. Accordingly, it is thought that during conditions promoting risk for infections (such as wounding) the body automatically increases its rate of innate responses, thereby limiting the risk of infection by surrounding microbes. Thus, the control of microbes is an integral part of normal bodily ‘housekeeping’. As such, the EGF-receptor-mediated innate immune response is a good example of a risk-limiting reaction. This discovery represents a major breakthrough for the Lund investigation.
In spite of the successful results that have already been accrued, along with the elaborate hypotheses and plans for further investigation, the study of skin innate immunity is not always simple. Indeed, Sørensen has been faced with a number of difficulties which have restricted and obstructed some elements of the research. One major challenge presented itself due to the necessary use of mice as a means of experimentation: "In our age of knock-out mice, mice models have become a golden standard for validation of the biological significance of scientific findings," he reflects. Unfortunately, however, the EGF-receptor-dependent responses that the scientists observe in human skin and human keratinocytes are rather differently regulated in mice where, confusingly, the same responses are totally independent of the EGF-receptor. Thus, in order to combat this issue and make future research slightly easier, the group must work with human ex vivo models. Unsurprisingly, this step is likely to present additional challenges when it comes to proving the biological importance of future findings.

The innate immune response is an intrinsic part of the normal wound healing process – even in the absence of microbes.

FURTHER INVESTIGATION

Looking to build on their progress to date, under Sørensen’s direction, the collaborating scientists plan to further investigate the immunological importance and the molecular regulation of the EGF-receptor. Its significance will be examined both in terms of wound healing, as well as in chronic wounds. As yet, the team has been able to identify innate immunity genes that are expressed in acute human skin wounds, due to EGF-receptor activation.

Subsequently, they plan to see how these genes are expressed in chronic wounds – for example, chronic venous ulcers or diabetic wounds. Since the activation of the EGF-receptor is known to cause the production of chemoattractant cytokines, it is thought that a ‘chronic’ activation of the EGF-receptor may actually help to drive the inflammation in chronic wounds, instead of promoting wound healing. Interestingly, it has already been established that growth factors fail to promote wound healing in chronic wounds. However, they are yet to demonstrate whether this outcome is perhaps due to the inflammatory side effect, or because the chronic wounds might already be overly stimulated with growth factors.

More ambitious still, is the ongoing analysis of the functions of the EGF-receptor with regard to its potential for cancer treatment – namely how EGF-receptor inhibition could complement the body’s own killing of cancer cells. The logic behind this line of investigation is that activation and overexpression of the receptor plays a key role in many cancers. If this project continues as successfully as it has begun, there exists the potential for the development of new treatment strategies for cancer.