Published in final edited form as:

Cytokine. 2015 June ; 73(2): 309–310. doi:10.1016/j.cyto.2015.03.008.

Introduction to a Special Issue on Skin disease, Immune Response and Cytokines

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Keywords

Special Issue; Skin; Inflammation; Cytokines; Introduction

Skin is the largest and fastest growing organ of the body. In recent years, attention has been directed towards the numerous ways in which immune cells of the skin interact with keratinocytes (KCs) to drive a multitude of skin diseases. Both resident immune cells and skin infiltrating cells can work synergistically with KCs to propagate disease pathogenesis. Activated KCs produce chemokines that recruit immune cells into the skin, which then initiate cascades of cellular and molecular events that are clearly responsible for the chronic nature of many inflammatory skin diseases. The concept that many skin diseases have a critical immune system component, or are auto-immune in nature, is now well accepted. The outdated debate regarding whether skin disease is KC-driven vs. immune cell-driven has evolved to include a more integrated conceptualization that encompasses pathways linking KC dysfunction with immune cell pathologies that synergize to create and sustain chronic cutaneous inflammation.

The anatomy of the skin under non-pathological conditions contains a collection of cells that are organized into layers, with the outer most layer being the epidermis, overlying the dermis, which sits above a layer of subcutaneous tissue called the hypodermis or subcutis. Resident cells comprise each of the three tissue layers; these include but are not limited to KCs, Langerhans cells, and nerve endings (epidermis); ECM-secreting fibroblasts, blood vessels and lymphatic vessels, blood vessel-related pericytes, nerves, and resident immune cells (dermis). These cells surround the hair follicles, the sebaceous glands and sweat glands, as well as the arrector pili muscle. The subcutaneous tissue is comprised mostly of fat and forms the pipeline in which the veins, arteries and nerves run through before branching and sprouting into the higher levels of skin.

During pathological events, whether chronic disease, an acute response to skin challenge, or a wound, the skin strategically mounts a response to elicit healing. This usually involves a series of tightly coordinated events between different cells, different cellular layers, and via contact and non-contact-mediated mechanisms. Soluble factors including cytokines, growth factors and chemokines derived from the resident skin cells signal to each other and initiate

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innate and adaptive immune responses. Antigen presenting cells in the skin capture antigen, traffic out of the tissue to skin draining lymph nodes, and present antigen to T cells, which clonally expand and traffic back to the skin where they continue to proliferate. The recruitment of lymphocytes results in activation of KCs, which results in additional recruitment of immune cells, thereby amplifying the inflammatory process. Under normal circumstances, when skin recovers from an acute challenge or injury, cutaneous immune responses are self-limiting and the skin returns to a quiescent state. However, when these events go awry, as in the case of a genetically susceptible population of patients, normally self-limiting cellular pathways and interactions become chronic and lead to disease pathogenesis. The critical contribution of immune system dysregulation and pro-inflammatory cytokines to chronic skin disease is evidenced by the efficacy of drugs, both topical and systemic, that target either immune cells directly, or their secreted molecules.

In this special issue of *Cytokine*, leading experts in inflammatory skin diseases present and discuss the role of immune cells, the immune system and pro-inflammatory cytokines in the pathogenesis of a variety of skin diseases, some of which are well accepted as “immune-driven” or immune-centric, while others are only now beginning to be understood as immunogenic in nature. Introduction to each of the diseases, their pathogeneses, and the individual contributions of immune cell subsets and specific cytokines are provided. Moreover, efficacy of newly developed drugs targeting these molecular and cellular players is discussed.

This issue begins with Emma Guttman-Yassky and Dana Malajian providing a cutting-edge review detailing how atopic dermatitis (AD) is now thought to be an immune-centric disease. Using the success of anti-IL-4R antagonist in the treatment of AD patients, they present a solid argument for the necessity of cytokines and the immunocytes secreting them as the cellular instigators of AD. They take the reader from the genetic basis of this disease to a discussion of the importance of skin commensals, barrier function alterations in the epidermis, finally focusing on immune abnormalities and the “inside-out” hypothesis.

This work is followed up by that of Ally-Khan Somani, Ashish Arshanapalli, Mihir Shah and Vindhya Veerula, who introduce readers to dermatomyositis (DM), a type I interferon (IFN)-driven disease with a critical role for immune cells. Their comprehensive review includes a summary of the last ~70 years of literature on this subject and provides insight into the clinical aspects of DM, detailing the importance of IFN signaling in disease pathogenesis. They also identify emerging roles for Th17 cells and interleukins (IL-17 and IL-6) in DM pathogenesis. Given the clinical success of currently available biologics targeting these cytokines in other diseases, it will be interesting to ask whether these agents can be used in the future as novel treatment approaches for DM patients.

Following the discussion of IFNs in DM, Victoria Werth and Elizabeth Robinson provide a thorough summary regarding the complexity of cytokine contributions to cutaneous lupus erythematosus (CLE) pathogenesis, including a role for IFN signaling and ultraviolet light. Within this review, the significance of communication between epidermal KCs and infiltrating immune cells is readily apparent. Moreover, the authors discuss recent interesting and paradoxical findings that pro-inflammatory cytokines, specifically TNF α , can exert

opposing effects on disease severity, such that elevated levels are critical for disease pathogenesis, yet TNF α inhibition can also produce new CLE-like symptoms.

The idea that cytokines can be “double-edged” in nature is further explored when Aimee Payne, Michael Cho and Christoph Ellebrecht discuss the role for IL-10 in pemphigus vulgaris (PV). Similar to themes raised in the other reviews in the current issue, cell-cell interactions between the different layers of the skin, in particular the KCs and the infiltrating immune cells, are critical in PV, an autoimmune blistering disease of the skin. The authors present an inclusive summary of the role of IL-10 in PV, from IL-10 genetic polymorphisms in PV patients, to animal models of pemphigus and effects of IL-10 manipulation, to a role for IL-10 in IgG4 class switching and potential contributions of IL-10-secreting T cells and B cells. Finally, they discuss the potential for IL-10 as a targetable cytokine for treating PV patients and the paradoxical, dual nature of this cytokine. They make a convincing argument that targeting IL-10 may not be the most beneficial strategy for treating PV patients, and they offer a transparent discussion of the need to further clarify the role of IL-10 in PV.

Finally, this special edition concludes with a discussion of psoriasis vulgaris, a relatively common skin disease with a known immune component. Andrew Johnston, Drew Barnes and Jaymie Balliwag give a comprehensive review of psoriasis pathogenesis, including a detailed overview of the contributions of IL-1 family members. They also discuss the nuances of IL-13, specifically how it may not fall neatly into the Th2 cytokine classification, and provide a great overview of the IL-12/23-Th1/Th17 axis of inflammation and how it's critical for psoriasis. To round out their discussion, they also discuss contributions of IFNs and TNF α in disease pathogenesis.

Importantly to all diseases discussed in this focus issue, the skin represents a unique organ system that can readily be studied, as it's visible and easily accessible. Importantly for dermatological research, obtaining fresh tissue to study is much easier than biopsying other organ systems, leading to unique opportunities to study human disease directly.

Indeed, the cellular interactions and molecular events driving many skin diseases are not unique to skin disease, but rather occur in similar configurations in other organ systems where epithelial-immunocyte interactions exist. The intestinal tract and lung are examples of such systems in which epithelial-immune interactions are critical for eliciting and sustaining chronic inflammation. Moreover, the IL-23/Th17-TNF α axis of inflammation is well understood to contribute to other chronic inflammatory conditions including Crohn's disease (CD), rheumatoid arthritis (RA), and multiple sclerosis (MS), where access to diseased tissues is challenging and the evaluation of clinical improvement is not as straightforward as looking at resolution of skin involvement. Psoriasis is a clear example of a skin disease which is leading to great insight into the basic immunological concepts that may enhance our understanding of other diseases, such as MS and RA; where obtaining tissues for study can prove more challenging; AD may also provide useful insight into other Th2-driven diseases that are less “visible,” such as asthma. The ability to understand skin disease pathogenesis and the subsequent impact this knowledge can exert outside the field of cutaneous biology is significant and will undoubtedly continue well into the future.

I am hopeful that this special issue of Cytokine, with a focus on the role of inflammation in skin disease, will serve as a valuable tool in deepening the reader's knowledge and appreciation for the complexity of skin diseases and the significant role played by the immune system. Ways in which immune cells and their cytokines operate in concert with epidermal KCs are directly advancing the field by uncovering novel treatment strategies. As clinicians and scientists become more well-versed in how individual genomes influence immune cell outcomes, the concept of personalized medicine will continue to evolve. I foresee this occurring within the fields of psoriasis and psoriatic disease, in which many genetic variants are well described and the criticality of several key cytokine pathways is well established. As we determine why some patients respond to some biological treatment approaches and others do not, forward movement in the realm of personalized medicine will occur.

I fully acknowledge that this issue fails to include many other skin diseases that also have significant contributions from the immune system, auto-immunity and immune cell interactions with key skin cells, including diseases such as alopecia areata, scleroderma, melanoma, and other types of skin cancers as well as cutaneous T cell lymphoma. It is my hope that these other areas of high interest will be covered in a subsequent review in the near future. I would like to thank all of the authors of the papers included in this special issue for providing well written, detailed, and comprehensive articles in a timely manner, and am grateful for their participation in this, and taking the time from their busy schedules to be a part of this edition.

Acknowledgments

This work was supported in part by awards from the National Institute for Arthritis, Musculoskeletal and Skin Diseases (P30 AR39750, R01 AR063437; R01 AR062546; and R21 AR063852) and by the Lozick Discovery Grant from the National Psoriasis Foundation. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.