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Role of epigenetics in the regulation of immune functions of the skin

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Abstract

This review is intended to illuminate the emerging understanding of epigenetic modifications which regulate both adaptive and innate immunity in the skin. Host defense of the epidermis and dermis involves the interplay of many cell types to enable homeostasis, tolerance to the external environment and appropriate response to transient microbial, chemical and physical insults. To understand this process, the study of cutaneous immunology has focused on immune responses that reflect both adaptive learned and genetically programed innate defense systems. However, recent advances have begun to reveal that epigenetic modifications of chromatin structure also have a major influence on the skin immune system. This deeper understanding of how enzymatic changes in chromatin structure can modify the skin immune system and may explain how environmental exposures during life, and the microbiome, lead to both short-term and long-term changes in cutaneous allergic and other inflammatory processes. Understanding the mechanisms responsible for alterations in gene and chromatin structure within skin immunocytes could provide key insights into the pathogenesis of inflammatory skin diseases that have thus far evaded understanding by dermatologists.

Introduction

External structures of all organisms have evolved adaptions that permit tolerance to their normal environment while also permitting rapid immune defense to limit dangers such as microbial infections. Immunological adaptations in this system occurs throughout life. When functioning properly this leads to improved defense against dangerous antigens and better tolerance to molecules that do not pose a risk to health. The cell biology and genetics of this system have become increasingly well understood. However, changes in skin immune function are not entirely explained by inheritable genetic information. To better understand

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R.L.G. is a co-founder, scientific advisor, consultant and has equity in MatriSys Biosciences and is a consultant, receives income and has equity in Sente Inc.

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skin immunology and disease it is necessary to improve understanding of how an individual environment can alter expression of gene products that shape the immune system.

A major mechanism for control of any gene is its chromatin structure. Chromatin structure is influenced by several factors including modifications made to histones, a core component of chromatin (Zhang and Cao, 2019). A great deal of progress has been made into understanding how environmental stimuli can lead to changes in chromatin structure (Lio and Huang, 2020) (Feil and Fraga, 2012) (Bar-Sadeh et al., 2020). This process of alterations in gene expression by changing chromatin structure rather than intrinsic changes in the genetic code itself is known as epigenetics. Epigenetic changes influence chromatin structure by chemical modification, which has a striking impact on gene expression (Jaenisch and Bird, 2003). Many different environments have been shown to have epigenetic influence on gene function including high altitude (Julian, 2017), hypoxia (Brown and Rupert, 2014), psychological stress (Bartlett et al., 2017), and exercise (Landen et al., 2019).

Cutaneous biologists have made many important contributions to the fundamental understanding of epigenetics and human health in the context of cell development and tumor biology (Köhler and Rodríguez-Paredes, 2020) (Botchkarev, 2017). However, the effects of epigenetic modifications on skin immune function have not been as extensively investigated. Our goal in this review is to present an overview of current knowledge of epigenetic mechanisms that are relevant to skin immune responses. As the reader will note, conclusions regarding the role of epigenetics in immune function depend on various factors. The techniques used to assess the response and the cell type and type of epigenetic modification are important variables that can drive alternative interpretations. We hope that summarizing this information for skin immunologists will help to focus and speed research in this field and perhaps further advance therapeutics of inflammatory skin disorders.

Types of epigenetic modifications

There are several different mechanisms for epigenetic modification of chromatin structure that have been associated with immune reactions. These include histone acetylation, histone methylation, histone SUMOylation, histone phosphorylation, histone ubiquitination, histone citrullination, histone lactylation, and DNA methylation. We begin by first providing brief definitions of each class of epigenetic modification.

Histone acetylation

Positively charged histones contact and wrap negatively charged DNA into the nucleosome (Grunstein, 1997). The lysine-rich domains in the amino-terminal tails of histone are targets for acetylation. Once acetylation occurs, the positive charge in these domains are neutralized. This can result in less condensed chromatin and activation of gene expression (Hogg et al., 2020) (Zhang and Cao, 2019)).

Histone methylation

Histone H3 is the primary target of histone methylation and this modification, especially methylation of lysine, can cause both induction and repression of gene expression. Although there are many exceptions, typically gene activation is promoted by methylation at H3K4,

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H3K36, and H3K79, while gene-repression occurs by methylation at H3K9 and H3K27 (Jambhekar et al., 2019).

DNA methylation

DNA methylation targets DNA regions where a cytosine nucleotide is followed by a guanine nucleotide in a linear sequence from a 5' to 3' direction. This "CpG island" is often found in promoters sites of genes and DNA methylation typically results in gene silencing (Poli et al., 2020).

Histone SUMOylation

The small ubiquitin-related modifier (SUMO) is a ubiquitin-like protein involved in gene transcriptional modifications (Johnson and Gupta, 2001) (Melchior, 2000). SUMO can attach to other proteins, leading to the activation of an enzyme cascade. Histone SUMOylation is most often associated with transcriptional repression.

Histone phosphorylation

Histone phosphorylation takes place mainly at serine, threonine, and tyrosine residues (Qin et al., 2020). Phosphorylation disrupts the interaction between histones and DNA and contributes to the instability of chromatin structure.

Histone ubiquitination

Histone H2A and H2B are sites targeted by ubiquitination. Ubiquitination at H2A and H2B are located near the entry site of DNA into the nucleosome. Therefore, ubiquitination can change chromatin structure and access of other enzymes involved in gene transcription. This histone modification plays critical roles in both transcriptional activation or inhibition (Hofmann, 2009).

Histone citrullination

Histone citrullination regulates gene expression by antagonizing further methylation of DNA (Cuthbert et al., 2004). A methyl group in DNA can bind to an arginine site on histone, affecting binding DNA to histone, resulting in transcriptional activation. Citrullination enzyme PAD converts this arginine site to citrulline and inhibits further histone methylation to repress gene transcription.

Histone lactylation

Lactate regulates physiological and pathological functions of immune cells, and accelerates the lactylation of histone lysine residues, and directly affects transcription. This recently reported histone modification accelerates inflammatory gene transcription in macrophages (Zhang D. et al., 2019).

Functional consequences of epigenetic modifications are cell-type specific

Adding to the complexity of the diverse epigenetic modifications that influence gene function is the observation that the functional consequence of these modifications cannot be

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universally applied to all cells of the immune system. Different cell types have been shown to respond very differently to similar epigenetic changes (Choi et al., 2018) (Turgeon et al., 2014) (Cao et al., 2014) (Pham et al., 2018) (Sanford et al., 2016) (Li X. et al., 2017) (Malinczak et al., 2020) (Kobatake et al., 2020). This results in increased expression of pro-inflammatory cytokines by some cells types and repression of the expression of inflammatory mediators by other cell types (Figure 1). For example, the effect of HDAC8 and HDAC9 is opposite in keratinocytes compared to macrophages. Inhibition of HDAC8 or HDAC9 will increase cytokine release in response to TLR activation of keratinocytes but will suppress cytokine responses from macrophages (Sanford et al., 2016). These alternative responses make sense when one considers the immunological context of the cell within the skin. For example, keratinocytes are in frequent contact with pathogen associated molecular patterns (PAMPs) or danger associated molecular patterns (DAMPs) and therefore may employ epigenetic mechanisms to tolerate frequent exposure. In contrast, cells deeper in the dermis such as macrophages may use the same epigenetic exposure to increase their capacity to promote inflammation. Other examples of this opposing response of epithelial cells and bone-marrow derived cells is seen with the histone demethylase KDM6A which positively regulates inflammatory cytokine production by macrophages but suppresses responses by epithelial cells from other organs (Choi et al., 2018) (Turgeon et al., 2014) (Cao et al., 2014) (Pham et al., 2018) (Li X. et al., 2017) (Malinczak et al., 2020). (Kobatake et al., 2020). In macrophages, KDM6A-knockdown reduces IL-6 and IFN-β (Li X. et al., 2017), and a KDM6 inhibitor reduces IL-6 in dendritic cells (Malinczak et al., 2020), but KDM6A-deficient urothelium has increased IL-6 (Kobatake et al., 2020). These different responses reflect the complexity of an incompletely understood system. One explanation for alternative responses that are cell type dependent is the presence of the corepressor and the nucleosome remodeling and deacetylase (NuRD) in macrophages. The NuRD complex negatively regulates inflammatory gene expression in macrophages (Ramirez-Carrozzi et al., 2006) (Musselman et al., 2009) but is not active in keratinocytes (Sanford et al., 2016). Epigenetic activation of genes that increase NuRD function will lead to repression of inflammation. In contrast, epigenetic activation of genes encoding inflammatory cytokines will increase inflammation. Thus, in this example, an epigenetic change that increases gene transcription can be either pro-inflammatory or anti-inflammatory. To best understand the potential influence of epigenetics on immunity we will next describe observations based on the cell type in which the experiments were performed.

Macrophages/Dendritic Cells

Macrophages and dendritic cells (DCs) have central roles in immunity and often dictate the direction of responses for other immune cells. Expression of MHC class II and costimulatory factors CD80 and CD86 have an important role in antigen presentation and are positively regulated by histone demethylation (Malinczak et al., 2020). Histone deacetylation by HDAC2, HDAC6 inhibits expression of these genes (Adeegbe et al., 2017, Kong et al., 2009), whereas SIRT1 positively regulates antigen presentation (Woo et al., 2016). Histone phosphorylation and citrullination increases expression of inflammatory cytokines such as TNF-α, IL-1β, and IL-6, (Leng et al., 2009, Marwick et al., 2015, Yang et al., 2008) (Josefowicz et al., 2016), lactylation (Zhang D. et al., 2019) (Mishra et al., 2019, Sohn et al., 2015, Wu et al., 2020) (Mishra et al., 2019, Suzuki et al., 2016). On the contrary,

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SUMOylation contributes to the suppression of inflammatory cytokine production (Jennewein et al., 2008).

Observations of the immunological consequences from enzymes with opposite actions in DC or macrophages include histone acetylation, methylation, ubiquitination, and DNA methylation. This further complicates conclusions regarding the role of epigenetic modifications to alter function in these cell types. Some apparently contradictory observations may also reflect the specific sites or genes in the chromosome that are targeted by these enzymes. For example, positive regulation of inflammatory cytokine production is seen with histone acetylase; p300/CBP (Peng et al., 2019, van den Bosch et al., 2016)) and histone deacetylases; HDAC1 (Cantley et al., 2015, Choi et al., 2018), HDAC7 (Das Gupta et al., 2020, Shakespear et al., 2013), HDAC9 (Cao et al., 2014, Li et al., 2016, Pham et al., 2018), HDAC11 (Wang et al., 2018), and SIRT4 (Li et al., 2019)). Other histone acetylases negatively regulate inflammatory cytokine production (KAT8 (Huai et al., 2019)) (SIRT2 (Lo Sasso et al., 2014), SIRT3 (Traba et al., 2015), and SIRT6 (Lee et al., 2017)). Furthermore, inflammatory responses can differ depending on the method of targeting enzymes responsible for epigenetic modifications (Fang et al., 2018, Kaneko et al., 2018) (Sanchez et al., 2018) (Pham et al., 2016) (Lu et al., 2015) (Li Z. et al., 2017, Poralla et al., 2015) (Jan et al., 2017) (Lu et al., 2015, Moreno-Gonzalo et al., 2017, Zhang W. B. et al., 2019) (Das Gupta et al., 2020) (Wang et al., 2018) (Jan et al., 2017) (Sano et al., 2018) (Yang et al., 2014) (Qin et al., 2017) (Wang et al., 2017) (Sun et al., 2016) (Kitamura et al., 2017). These findings show specificity in targeting epigenetic modifications is important to understand therapeutic efficacy.

T cells

As classical immunocytes the many different T-cell subsets play a critical role in cutaneous immunity. Deubiquitination of histones and DNA methylation in T cells can promote their expansion (Dufner et al., 2015)) (Lee et al., 2001) (Manna et al., 2015). Histone acetylation and methylation have also been reported to positively regulate T cell development (Gao et al., 2017) (Göschl et al., 2018) (Boucheron et al., 2014) (Philips et al., 2016) (Takikita et al., 2016, Toubai et al., 2018) (Long et al., 2020). Th1 cells are positively driven by citrullination (Liu Y. et al., 2018), while negatively regulated by DNA demethylation (Carty et al., 2018). Depending on the methodology used, histone methylation can promote both directions in Th1 development with positive actions by EZH2 (He et al., 2017) and MLL1 (Schaller et al., 2015), and negative regulation of $CD8^+$ T cell differentiation and long-term memory reprogramming capacity in $CD8^+$ cells by SUV39H1 (Pace et al., 2018).

Th1 cytokines are positively regulated by DNA methylation (Nakatsukasa et al., 2019) (Ichiyama et al., 2015)). Histone demethylases (JMJD3 (Li et al., 2014), LSD1 (Liu W. et al., 2018), KDM6A (Itoh et al., 2019), UTX (Kruidenier et al., 2012), and OCA-B (Shakya et al., 2015)) and histone methyltransferases (G9a (Antignano et al., 2014), EZH2 (He et al., 2013) also positively regulate Th1 cytokine production.

HDACs and deubiquitinases exhibit opposite inflammatory actions depending on each enzyme in T cells. Th1 cytokines are positively regulated by HDAC6 (Tsuji et al., 2015), HDAC9 (Yan et al., 2011), and HDAC11 (Yuan et al., 2018)), whereas HDAC1 has the

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opposite effect (Göschl et al., 2018). Deubiquitination by USP16 (Zhang Y. et al., 2019) and USP18 (Honke et al., 2011) positively regulates inflammatory cytokine production, however, OTUB1 and USP15 show opposite effects (Zhou et al., 2019, Zou et al., 2014).

Th2 cells exacerbate allergic inflammation mediated by IL-4, IL-5, IL-12, and IL-13, and the importance of these cytokines in allergic cutaneous immunity is proven by the current treatment of targeted therapy for these cytokines (Beck et al., 2014). Th2 is positively driven by phosphorylation (Bhattacharya et al., 2011) (Blüml et al., 2009) and histone methylation (Adoue et al., 2019)). Histone deacetylation, histone deubiquitination, DNA methylation, histone demethylation basically suppress Th2 cytokine production (Jang et al., 2016, Yan et al., 2011) (Yuan et al., 2018) (Guo et al., 2017) (Makar and Wilson, 2004) (Li et al., 2014) (Grausenburger et al., 2010) (Zhang et al., 2009).

Th17 are involved in various inflammatory skin diseases and the downstream pathway promotes neutrophil function. Psoriasis is a representative Th17-mediated skin disease and IL-17-targeted biologics are efficient therapies (Langley et al., 2014). Th17 development and its cytokine production are positively driven by citrullination (Liu Y. et al., 2018, Seri et al., 2015)), phosphorylation (Li et al., 2011), and deubiquitination (Han et al., 2014) (Liu X. et al., 2013). DNA demethylation promotes Th17 development by TET2 (Ichiyama et al., 2015), however, negatively regulates these function by TET2/3 (Nakatsukasa et al., 2019). DNA demethylation, histone deacetylation, and SUMOylation show different effects depending on targeted epigenetic enzymes (Nakatsukasa et al., 2019)(Ichiyama et al., 2015) (Lim et al., 2015) (Gardner et al., 2013) (Yan et al., 2017) (He et al., 2018, Singh et al., 2018). Histone methylation negatively regulates IL-17 production (Antignano et al., 2014), while histone demethylation also showed both positive/negative regulation of Th17 development (Itoh et al., 2019) (Cribbs et al., 2020) (Li et al., 2014) (Liu W. et al., 2018) (Liu et al., 2015).

Tregs have potent capacity to regulate many inflammatory responses (Wing et al., 2019). Treg development and function are positively regulated by DNA demethylation (Nakatsukasa et al., 2019, Yang et al., 2015) (Kim and Leonard, 2007) and histone acetylation (Liu Y. et al., 2013) (>Liu et al., 2014). HDAC3 has shown positive regulation of Treg development (Wang et al., 2015)). The contribution of SIRT1 on Treg function is still controversial and depends on the treatment approach (Daenthanasanmak et al., 2019) (Martin et al., 2018). Histone methylases/demethylases and deubiquitinase show different effects on Tregs depending on each enzyme (Antignano et al., 2014, Nagata et al., 2015, Wang et al., 2016)) (Zou et al., 2015) (Cribbs et al., 2018) (Sarmento et al., 2017, Wang et al., 2013) (Doñas et al., 2016).

Epithelial cells

Epithelial cells are not considered classical immunocytes but have become increasingly appreciated as a critical cell type for regulation of immunity (Honda et al., 2013) (Zhang et al., 2016) (Luger and Schwarz, 1990). Keratinocytes, as the primary epithelial cell in the skin, influences immune responses by both direct expression of cytokines and antimicrobial peptides and by indirect functions as a barrier between the environment and classical immunocytes. As limited information is available that has specifically looked at epigenetic

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regulation of keratinocyte immune function, this section will also highlight observations from epithelial cells in other organs.

Different HDACs have been reported to negatively regulate inflammatory cytokine expression by epithelia (HDAC1 in intestinal epithelial cells (Turgeon et al., 2014), HDAC2 in intestinal epithelial cells (Turgeon et al., 2014), HDAC8 in keratinocytes (Sanford et al., 2016), HDAC9 in keratinocytes (Sanford et al., 2016), SIRT3 in bronchial epithelial cells (Chen et al., 2016), and SIRT6 in keratinocytes (Zhang et al., 2018) and kidney tubule epithelial cells (Gao et al., 2020)). Histone demethylase KDM6A has shown activity in urothelium (Kobatake et al., 2020), histone methyltransferase G9a in keratinocytes (Li et al., 2018) and SETDB1 in intestinal epithelial cells (Južnić et al., 2020). Inflammatory cytokines have been also shown to be positively regulated by HDAC3 in intestinal epithelial cells (Navabi et al., 2017), HDAC5 in bronchial epithelial cells (Luo et al., 2019), and HDAC6 in bronchial epithelial cells (Lin et al., 2020). Histone demethylation enzymes, JMJD3 and SET7/9, positively regulate the production of antimicrobial peptides by keratinocytes (Gschwandtner et al., 2014) and inflammatory cytokines by bronchial epithelial cells (He et al., 2015), respectively. Citrullination increases inflammatory cytokine and chemokine production by renal tubule cells (Ham et al., 2014). A DNA demethylase, TET1, enhances inflammatory cytokine production by keratinocytes (Ryu et al., 2019). The role of SIRT1 on inflammatory cytokine production is controversial when studied by silencing in bronchial epithelial cells (Tang et al., 2017), gingival epithelial cells (Minagawa et al., 2015), and retina epithelial cells (Xiao and Liu, 2019). Overexpression of SIRT1 reduces inflammatory responses by keratinocytes (Wang et al., 2019).

Epigenetic modulation of inflammatory skin diseases

Some reports have focused on the impact of epigenetic changes in inflammatory skin disease, but much more research is needed to understand how modifications of chromatin structure in multiple cell types translates into disease. The following briefly summarizes some key conclusions by the disease in which the observations were made.

Contact dermatitis is a Th1-mediated inflammatory skin disease and DC-T cell interactions influence the development of skin inflammation in this disorder. Little is known about the contribution of epigenetic modifications in contact dermatitis. Topical butyrate has been reported to reduce contact hypersensitivity responses through increased number of Foxp3-positive cells in the sodium butyrate-treated skin (Schwarz et al., 2017).

Atopic dermatitis is a representative of a Th2-mediated chronic allergic inflammatory disease. Pan-HDAC inhibition by trichostatin A negatively regulates atopic inflamed skin in mice (Kim et al., 2010). On the other hand, SIRT1 preserved skin barrier function in atopic dermatitis (Ming et al., 2015).

Psoriasis is a representative of a Th17 mediated inflammatory skin disease. SIRT1 is decreased in psoriatic skin, while SIRT6 is increased. This has a positive correlation with detection of inflammatory cytokines (Rasheed et al., 2016). There are several reports to evaluate the actual impact of epigenetic modifications on psoriatic skin lesions. SIRT1 and

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SIRT2 negatively regulate psoriatic skin inflammation, and psoriasiform skin inflammation was aggravated by SIRT1 inhibition (Xie et al., 2015) and Sirt2-deficiency (Hao et al., 2020). As an overall impact of HDAC inhibition, topically applied sodium butyrate reduced imiquimod-induced inflammation and downregulated IL-17 and induced IL-10 and FOXP3 transcripts (Schwarz et al., 2020).

A constitutive source of inhibitors for HDACs is the presence of short-chain fatty acids such as butyrate produced by *C. acnes* when growing under fermentation conditions in hair follicles (Shu et al., 2013). Short-chain fatty acids produced by *C. acnes* inhibits HDACs in keratinocytes. Inhibition of HDAC8 and HDAC9 in keratinocytes and sebocytes greatly increases the release of inflammatory cytokines after exposure to TLR ligands (Sanford et al., 2019, Sanford et al., 2016). These observations may be a clue to the pathogenesis of acne vulgaris and provides a mechanism for the microbiome to regulate immune functions through an epigenetic mechanism.

Future directions

The role of epigenetics in cutaneous immunity still remain largely unknown. As this brief review has summarized, there are abundant existing observations suggesting that control of gene expression by epigenetic events can influence immune functions. It is tempting to speculate that by understanding the role of epigenetics in skin immunity it may be possible to explain and/or reverse the development of chronic inflammatory disorders that have not shown major associations with whole genome DNA sequence analysis. However, the current state of this field requires much more work to accurately interpret the significance of past observations. Epigenetic enzymes can have opposite inflammatory responses that depend on the treatment, and this leads to the difficulty to understand the real function of these enzymes. Elucidation of immune cell function by specific cell-targeted assessment of specific enzymes is desired to get a better understanding of the mechanisms of epigenetic regulation important to skin immunity. Such studies can lead to validation of the role of these systems *in vivo* and successful interventional trials to treat inflammatory skin disorders.

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Figure 1. Opposing influence of epigenetic modifications on gene expression by different cell types that participate in the immune response of the skin.

Illustration to list epigenetic modifications that have been reported in each indicated cell type. References are organized to indicate if these modifications have been reported to result in evidence of cell activation or gene repression.