Journal of Dermatological Science xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Dermatological Science

journal homepage: www.jdsjournal.com

Histone modifiers: Dynamic regulators of the cutaneous transcriptome

Kanad Ghosh[a], Kyle O'Neil[a], Brian C. Capell[a,b,*]

[a] Penn Epigenetics Institute, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, 19104, USA
[b] Departments of Dermatology and Genetics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, 19104, USA

ARTICLE INFO

Article history:
Received 24 August 2017
Received in revised form 2 December 2017
Accepted 14 December 2017

Keywords:
Histone modification
HDACs
Chromatin
Epigenetics
Skin cancer
Wound healing
Epidermal differentiation

ABSTRACT

By regulating the accessibility of the genome, epigenetic regulators such as histone proteins and the chromatin-modifying enzymes that act upon them control gene expression. Proper regulation of this "histone code" allows for the precise control of transcriptional networks that are essential for establishing and maintaining cell fate and identity, disruption of which may drive carcinogenesis. How these dynamic epigenetic regulators contribute to both skin homeostasis and disease is only beginning to be understood. Here we provide an update of the current understanding of histone modifiers in the skin. Indeed, as one of the most innovative and rapidly expanding areas in all of medicine, it is clear that epigenome-targeting therapies hold great promise for the treatment of dermatological diseases in the coming years.

1. Introduction

The cell nucleus contains roughly six feet of DNA if it was stretched from end to end. This remarkable feat is accomplished through the intricate organization of that DNA into chromatin. The organization and structure of chromatin can control gene expression. The study of chromatin, the changes it undergoes, and how these changes effect transcription fall under the umbrella of epigenetics, which refers to changes in gene expression caused by factors other than alterations in the nucleotide sequence. The fundamental unit of chromatin consists of DNA wrapped around protein octamers, termed histones, in 147 base pair segments to form nucleosome subunits. Histone octamers are made of two copies of each core histone: H2A, H2B, H3, and H4. These histones have positively charged amino (N)-terminal tails which extend from the nucleosome and can undergo several modifications, which in turn affect chromatin accessibility and gene expression. These modifications, including acetylation, methylation, and ubiquitination, among others, and are regulated by various chromatin-modifying enzymes, frequently referred to as "writers" and "erasers," which are responsible for incorporating or removing modifications, respectively. In addition to histones, writer and eraser proteins can also interact with transcription factors and other proteins, allowing for an incredibly intricate and multilayered system for the fine-tuned regulation of gene expression.

Though research on epigenetic modifiers and histone modifications has been ongoing for decades and rapidly expanded in recent years, a vast amount remains unknown about the roles and effects of these modifiers in the skin. In this review, we discuss the current evidence for the role of these histone modifiers in the skin, with a particular focus on histone methylation and acetylation, given their status as the most abundant and well-studied histone post-translational modifications. Specifically, we delve into the current knowledge of histone acetyltransferases (HATs), histone deacetylases (HDACs), histone methyltransferases (HMTs), and histone demethylases (HDMs), the epigenetic writers and erasers that orchestrate acetylation and methylation, respectively, and how disruption of their normal function may promote disease in the skin.

2. Histone deacetylases

Zinc dependent histone deacetylases (HDACs), responsible for the removal of acetyl marks from histones and other protein substrates, are by far the most well-studied of the chromatin-modifying enzymes. They are broadly placed into four classes: Class I, including HDACs 1–3 and 8, Class II, including HDACs 4–7, 9, and 10, Class III, made up of Sirt1-7, and Class IV, containing HDAC11. The most well studied class of HDACs in the context of gene regulation are Class I deacetylases, which have been shown to

* Corresponding author. Departments of Dermatology and Genetics, Penn Epigenetics Institute, University of Pennsylvania, Biomedical Research Building 1007, Philadelphia, Pennsylvania 19104, USA.
E-mail address: brian.capell@uphs.upenn.edu (B.C. Capell).

https://doi.org/10.1016/j.jdermsci.2017.12.006
0923-1811/

Please cite this article in press as: K. Ghosh, et al., Histone modifiers: Dynamic regulators of the cutaneous transcriptome, J Dermatol Sci (2017), https://doi.org/10.1016/j.jdermsci.2017.12.006

have deacetylase and other unique chromatin remodeling activities. Both HDAC1 and HDAC2 have been shown to be critical during mammalian development [1]. HDAC2/3 induction, seen in HDAC1 knockout mouse embryonic stem (ES) cells, is not enough to compensate for loss of HDAC1[2], suggesting that although there is some overlap between HDAC1/2 activities, there are other unique functions that are specific to each.

HDAC1/2 is required for proper hair follicle and epidermal proliferation and differentiation[3]. Mice lacking HDAC1/2 in keratinocytes show increased expression of CDK inhibitors p21 and $p16^{INK4A}$. These cell cycle inhibitors are usually repressed via p63, a p53 family transcription factor, and HDAC1/2 is found to bind to the promoters of these CDK inhibitor genes in normal, undifferentiated keratinocytes [3]. Beyond cell cycle regulation, another Class I HDAC, HDAC3, is known to contribute to glucocorticoid receptor (GR)-mediated transcriptional repression, including reducing the expression of inflammatory genes in the skin, demonstrated through keratinocyte-specific ablation of HDAC3 in mice [4]. Thus, these Class I deacetylases play important roles in maintaining skin homeostasis (Fig. 1).

Regarding Class II HDACs in normal skin function, *in vitro* analysis of primary human skin fibroblasts has shown that HDAC4, and to a lesser extent HDAC6 and 8, are required for TGFβ1 mediated myofibroblast differentiation, an important aspect of wound healing [5]. Class III HDACs, the Sirtuin proteins, have also been associated with functions in normal skin, such as induction of keratinocyte differentiation, the inhibition of collagen degrading matrix metalloproteinases (MMPs), and decreasing DNA damage following UV exposure. Intriguingly, Sirtuin activation both by resveratrol as well as a synthetic activator decreased levels of HDAC2 and accelerated wound healing rates, an effect mimicked by HDAC inhibition by TSA [6]. These results indicate that different classes of HDACs are able to regulate the activity of others, leading to a complex interplay between deacetylases *in vivo*.

Considering the extensive evidence described above to demonstrate the role of HDACs in normal skin function, it is no surprise that various skin diseases are associated with the aberrant expression and function of these proteins. One of the emerging areas of study involves the roles of HDACs in skin cancer, where HDAC inhibitors are quickly becoming a well-documented therapeutic modality. In 1999, the pan-HDAC inhibitor trichostatin (TSA) was discovered to irreversibly arrest the growth of keratinocytes and squamous cell carcinoma (SCC) cells through the reduction of cyclin-dependent-kinase-1 (CDK1) transcription, indicating a potential therapeutic benefit in context of cancer [7]. Since then, HDAC inhibitors have demonstrated activity in melanoma, cutaneous T-cell lymphoma (CTCL), Merkel cell carcinoma (MCC) and other skin cancers (Fig. 1). The HDAC 1–11 inhibitors suberoylanilide hydroxamic acid (SAHA), valproic acid (VPA), and romidepsin are currently used in clinical settings, although it can be argued that specific inhibition of HDAC1/2 may be sufficient to produce therapeutic advantages [8]. In addition, several other potential mechanisms of action have been proposed to explain the therapeutic advantage of HDAC inhibition. For instance, extensive studies have shown that HDAC inhibitors induce cell cycle arrest through the upregulation of $p21^{WAF1/CIP1}$, the promotion of apoptosis, and inhibiting angiogenesis. In the skin, the HDAC inhibitor vorinostat was shown to inhibit tumor growth and proliferation in epidermoid carcinoma cells by reducing mTOR signaling [9], while HDAC inhibitors can also halt melanoma cell proliferation by repressing inositol polyphosphate 5-phosphatases which inhibit PI3 K/Akt mediated growth [10]. In addition to the potential of HDACs 1 and 2 to promote oncogenesis, there is also some evidence that both Sirt1 and Sirt3 can promote the initiation of melanoma [11,12]. However, the role of Sirtuins in cancer remains complicated, as Sirtuins have been categorized as both oncogenes and tumor suppressors, depending on the context [13–15]. Indeed, given the potential pleiotropic mechanisms driving HDAC-mediated tumorigenesis, further work will continue to dissect the major pathways involved and how they may be potentially targeted.

3. Histone acetyltransferases

Histone acetyltransferases (HATs) are protein complexes that transfer acetyl groups onto substrates such as the amino tails of histones and transcription factors. Through this mechanism, they are able to regulate chromatin structure by neutralizing the

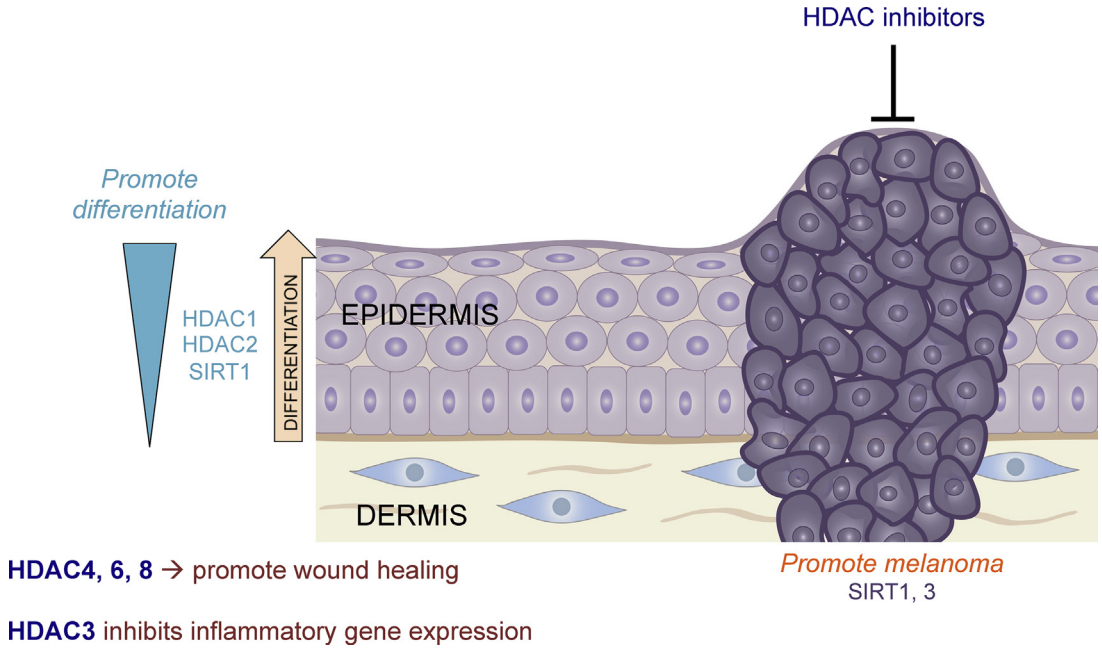

Fig. 1. Histone deacetylases (HDACs) display a diverse and enormously complex array of roles in the skin, not only promoting differentiation and wound healing, but also cancer in other contexts. Thus HDAC inhibitors have demonstrated evidence of efficacy for a number of cutaneous neoplasms.

Please cite this article in press as: K. Ghosh, et al., Histone modifiers: Dynamic regulators of the cutaneous transcriptome, J Dermatol Sci (2017), https://doi.org/10.1016/j.jdermsci.2017.12.006