necessarily represent the official views of the NIAMS or NIH.

REFERENCES

Bernink JH, Peters CP, Munneke M *et al.* (2013) Human type 1 innate lymphoid cells accumulate in inflamed mucosal tissues. *Nat Immunol* 14:221–9

Chang Y-J, Kim H, Albacker L *et al.* (2011) Innate lymphoid cells mediate influenza-induced airway hyperreactivity independent of adaptive immunity. *Nat Immunol* 12:631–8

Coccia M, Harrison OJ, Schiering C *et al.* (2012) IL-1beta mediates chronic intestinal inflammation by promoting the accumulation of IL-17A secreting innate lymphoid cells and CD4(+) Th17 cells. *J Exp Med* 209:1595–609

Gudjonsson JE, Thorarinsson AM, Sigurgeirsson B *et al.* (2003) Streptococcal throat infections and exacerbation of chronic plaque psoriasis: a prospective study. *Br J Dermatol* 149:530–4

Hedrick MN, Lonsdorf AS, Shirakawa AK *et al.* (2009) CCR6 is required for IL-23-induced psoriasis-like inflammation in mice. *J Clin Invest* 119:2317–29

Kim H, Lee H, Chang Y-J *et al.* (2014) IL-17 producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity. *Nat Med* 20:54–61

Neill DR, Wong SH, Bellosi A *et al.* (2010) Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. *Nature* 464:1367–70

Pantelyushin S, Haak S, Ingold B *et al.* (2012) Rorgammat+ innate lymphocytes and gammadelta T cells initiate psoriasiform plaque formation in mice. *J Clin Invest* 122:2252–6

Powell N, Walker AW, Stolarczyk E *et al.* (2012) The transcription factor T-bet regulates intestinal inflammation mediated by interleukin-7 receptor+ innate lymphoid cells. *Immunity* 37:674–84

Salimi M, Barlow JL, Saunders SP *et al.* (2013) A role for IL-25 and IL-33-driven type-2 innate lymphoid cells in atopic dermatitis. *J Exp Med* 210:2939–50

Sigurdardottir SL, Thorleifsdottir RH, Valdimarsson H *et al.* (2013) The association of sore throat and psoriasis might be explained by histologically distinctive tonsils and increased expression of skin-homing molecules by tonsil T cells. *Clin Exp Immunol* 174:139–51

Teunissen M, Munneke M, Bernink J *et al.* (2014) Composition of innate lymphoid cell subsets in the human skin: Enrichment of NCR+ ILC3 in lesional skin and blood of psoriasis patients. *J Invest Dermatol* 134:2351–60

Villanova F, Flutter B, Tosi I *et al.* (2014) Characterization of innate lymphoid cells in human skin and blood demonstrates increase of NKp44+ ILC3 in psoriasis. *J Invest Dermatol* 134:984–91

Zaba LC, Suarez-Farinas M, Fuentes-Duculan J *et al.* (2009) Effective treatment of psoriasis with etanercept is linked to suppression of IL-17 signaling, not immediate response TNF genes. *J Allergy Clin Immunol* 124:1022–30

See related article on pg 2371

Gene Regulation at a Distance: Higher-Order Chromatin Folding and the Coordinated Control of Gene Transcription at the Epidermal Differentiation Complex Locus

Michael Y. Fessing[1]

Chromatin structure and spatial interactions between proximal and distal gene regulatory elements, including gene core promoters and enhancers, are important in the control of gene transcription. In this issue, Oh *et al.* characterized an AP-1-dependent enhancer at the epidermal differentiation complex locus that establishes spatial interactions with numerous gene promoter regions at that locus.

Journal of Investigative Dermatology (2014) **134,** 2307–2310. doi:10.1038/jid.2014.247

[1]*Centre for Skin Sciences and School of Medical Sciences, School of Life Sciences, University of Bradford, Bradford, UK*

Correspondence: Michael Y. Fessing, Centre for Skin Sciences and School of Medical Sciences, School of Life Sciences, University of Bradford, Bradford BD7 1DP, UK. E-mail: m.fessing@bradford.ac.uk

All somatic cells in a multicellular organism share identical DNA content, but demonstrate vastly different phenotypes, as is required for tissue and organ development and homeostasis. Such differences are based on tissue-specific programs of gene expression established in multi-potent progenitor cells and their differentiating progenies. In mammals, gene expression programs are controlled at multiple levels, including gene transcription. Transcription of protein-coding and the majority of protein noncoding genes is regulated by binding of and interactions between numerous regulatory proteins, RNA polymerase II, and proximal and distal gene *cis*-regulatory elements. The best studied type of functional interaction between *cis*-regulatory elements is spatial contact between the gene core promoter and enhancer regions, which may be separated by hundreds of kilobase pairs, or they could even be located on different chromosomes (Bulger and Groudine, 2011; Harmston and Lenhard, 2013). Because DNA is organized in a nuclear–protein complex called chromatin, chromatin structural remodeling is required to control protein binding to the regulatory regions and to establish contact between the distal and proximal gene regulatory elements (Rando and Chang, 2009).

Proper higher-order chromatin folding in the three-dimensional (3D) nuclear space is important in establishing functional interactions between the promoters and enhancers involved in controlling cell-type–specific gene transcription for numerous genes, including Shh, as well as the genes that constitute the β-globin, α-globin, and Hox gene loci (Bulger and Groudine, 2011; Gibcus and Dekker, 2013). Genome-wide association studies have demonstrated that many single-nucleotide polymorphisms identified in the intergenic regions are associated with human diseases, suggesting that such defects might perturb normal gene expression programs by affecting distal gene *cis*-regulatory elements (Maurano *et al.*, 2012).

Functionally related and coregulated genes often form multi-gene loci in mammalian genomes. Genes involved in execution of keratinocyte-specific gene expression programs are clustered in at least three evolutionally conserved

Clinical Implications

- Many genetic defects associated with human disease are located in noncoding regions, and they involve gene enhancers and other distal gene regulatory elements.
- Characterization of the 923 enhancer and its target genes at the epidermal differentiation complex locus will provide new tools to understand genetic defects associated with skin disease.
- Combining new high-throughput methodological approaches to study correlations between genetic variations, gene expression programmes, and genome-wide chromatin structural states in defined populations of the cutaneous epithelial cells will provide new insight into the etiologies of skin disease.

regions, including the epidermal differentiation complex (EDC) and Keratin type I and type II loci. However, molecular mechanisms involved in coordinated gene regulation at these loci remain largely unknown. In this issue, Guzman-Strong and her team report on the characterization of the epidermis-specific enhancer 923 within the EDC locus (Oh *et al.*, 2014). They show that this enhancer has tissue-specific activity in transgenic mice and that it is active in both proliferating and differentiating murine keratinocytes in culture. Using chromatin conformation capture (3C) technology they demonstrate that this enhancer forms spatial interactions with the promoter regions of many genes within the EDC in primary keratinocyte cultures and that some, but not all, of these contacts depend on culture conditions (proliferative versus differentiating). Finally, their data reveal that binding of the AP-1 transcription factor to the enhancer region is important for enhancer element activity and establishment of some, but not all, spatial contacts with gene promoters.

Regulation of gene transcription by enhancers

Most regulatory information required for spatial and temporal control of gene transcription programs in metazoans is located outside core promoters within distal gene regulatory elements. Among these regulatory elements, the best studied are enhancers, which are DNA regions enriched in binding of transcription factors and chromatin remodelers that can increase transcription rates of target genes in a manner that is independent from distance to and orientation of the targeted promoter.

Several relatively common genetic and epigenetic features of enhancers allow their identification in the genome. They are frequently located in the noncoding elements that are highly conserved across different mammalian species (Bulger and Groudine, 2011; Harmston and Lenhard, 2013). This feature was used initially to identify the 923 enhancer characterized by Guzman-Strong's team (Oh *et al.*, 2014). Functional enhancers are usually located in the DNase I hypersensitive regions of chromatin because of the binding of multiple nonhistone proteins. In paused and active enhancers, there is a high level of mono-methylated lysine 4 in the histone H3 tail (H3K4me1), whereas active enhancers also show high levels of acetylated lysine 27 in the histone H3 (H3K27ac) (Bulger and Groudine, 2011; Harmston and Lenhard, 2013). Oh *et al.* (2014) demonstrated clearly that the 923 enhancer is active in epidermal keratinocytes, both *in vitro* and *in vivo*, and that this activity depends on the transcription factor AP-1.

One of the major questions in enhancer biology concerns the mechanisms that underlie the interaction between enhancers with target genes, and this highlights the importance of higher-order chromatin folding and spatial organization of genes and enhancers within the nucleus for the control of gene transcription.

Higher-order chromatin folding, 3D genome organization, and control of gene expression

Progress in the analysis of higher-order chromatin folding and 3D genome organization has been achieved using two approaches. The first is confocal microscopy after 3D fluorescence *in situ* hybridization or gene loci labeling in live cells using transgenic fluorescent chimeric proteins that contain specific DNA-binding domains (Cremer and Cremer, 2010). The second is 3C technology and its modifications, based on the restriction digestion of chromatin cross-linked using formaldehyde, followed by ligation at very low chromatin concentrations to allow the formation of intramolecular, but not intermolecular, products (Dekker *et al.*, 2013). The original 3C technology provides information about spatial interaction between two selected genomic regions, often referred to as a ''one versus one'' approach. The high-throughput modifications of this technology include circular chromatin conformation capture (4C) technology, allowing analysis of spatial interaction of a single genomic site with all other regions of the genome (''one versus all'' approach), chromatin conformation capture carbon copy (5C) technology, allowing analysis of spatial interactions between a set of selected genomic regions and another set of the selected regions (''many versus many'' approach), and Hi-C technology, providing information about interactions between all genomic regions (''all versus all'' approach) (de Wit and de Laat, 2012). These studies have revealed that chromosomes are organized into chromosome territories in the interphase nucleus and that many genes are not distributed randomly within the 3D nuclear space.

Accumulating evidence suggests that signaling/transcription factor–mediated and epigenetic gene regulatory mechanisms are intimately connected (Botchkarev *et al.*, 2012). In the developing epidermis, transcription factor p63 and ATP-dependent chromatin remodeler Brg1 are required for EDC locus relocation from the nuclear periphery toward the nuclear interior in epidermal progenitor cells (Mardaryev *et al.*, 2014). Furthermore, the global