Second International Symposium—Epigenetic Regulation of Skin Regeneration and Aging: From Chromatin Biology towards the Understanding of Epigenetic Basis of Skin Diseases

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After the First International Symposium on Skin Epigenetics at the University of Bradford (UK) in 2012 (Botchkarev et al., 2013), the research in this area has progressed substantially toward understanding how epigenetic regulatory machinery operates in concert with signaling pathways and transcription factors to control gene expression in normal skin and how epigenetic mechanisms are dysregulated in many pathological conditions including inflammatory skin disorders and cancer. To summarize recent achievements in skin epigenetics and to provide an opportunity for investigators to meet again and discuss the most important aspects of this rapidly expanding area, International Symposium "Epigenetic Regulation of Skin Regeneration and Aging" was held on March 17—19, 2016, in the Centre for Skin Sciences at the University of Bradford, UK. The Symposium was attended by over 110 participants from Europe, China, Japan, Singapore, and the United States, representing academic institutions as well as pharmaceutical and personal care industries. The Symposium program included eight Keynote lectures, the John M. Wood Memorial Lecture, and 27 talks organized into six sessions.

In the Opening lectures, Prof. Cheng-Ming Chuong (University of Southern California, Los Angeles) and Prof. Fiona Watt (King's College London, UK) introduced skin as an excellent model for epigenetic research, and Prof. Terumi Kohwi-Shigematsu (University of California, San Francisco) presented data on how epigenetic machinery contributes to neoplastic cell transformation. Following up the previous research on the role of DNA methyltransferase 1 in the control of hair follicle development and aging of mice (Li et al., 2012), Chuong described about how keratin genes are organized in the chicken genome. Similar to mammals, chicken keratin genes are clustered into distinct loci on chromosomes 25 and 27; whereas β-keratin genes on chromosome 25 show more inter-appendage differences in their expression, those on chromosome 27 show more intra-appendage differences, thus providing specific molecular targets for the study of epigenetic regulation (Wu et al., 2015). Watt described interplay between signaling and epigenetic mechanisms in the context of a recently discovered network of interactions involving different epigenetic regulators that affects two functionally related gene sets involved in the anchorage of epidermal stem cells to their niches (Mulder et al., 2012). Kohwi-Shigematsu discussed how the chromatin architectural protein and genome organizer SATB1 enables cells to change their phenotypes by regulating genes through higher-order chromatin reorganization and epigenetic modification in cancers of distinct cell types to regulate epigenetic modification, transcription, and drive metastasis (Kohwi-Shigematsu et al., 2012, 2013).

DNA AND HISTONE MODIFICATIONS AND THE CONTROL OF GENE EXPRESSION

DNA methylation/hydroxymethylation and different chemical modifications of the histone proteins play pivotal roles in the control of gene activation/silencing and promoter/enhancer interactions in epithelial stem cells and their progenies (Avgustinova and Benitah, 2016). Prof. Wolf Reik (Babraham Institute, Cambridge, UK) presented his work on mechanisms that regulate epigenetic reprogramming, which appears to be conserved in mammals and is essential for imprinting, transition to pluripotency, and the generation of induced pluripotent stem cells. His laboratory has identified signaling events that regulate DNA methylation dynamics during early development and that connect reprogramming firmly with naïve pluripotency; ongoing work is focused on the roles of these pathways in natural and experimental reprogramming (von Meyenn et al., 2016).

Prof. Salvador Benitah's laboratory (Institute for Research in Biomedicine, Barcelona, Spain) reported that de novo DNA methylation catalyzed by Dnmt3a and Dnmt3b occurs in human epidermal stem cells and their differentiated counterparts at the most active subset of enhancers in a histone H3K36me3-dependent manner. Both Dnmt3a and Dnmt3b bind to super-enhancers associated with genes that either define the ectodermal lineage or establish the stem cell and differentiated

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Abbreviation: HDAC, histone deacetylase

states: Dnmt3a is required to maintain high levels of DNA hydroxymethylation at the center of the enhancers, and Dnmt3b is necessary to maintain high levels of DNA methylation along the enhancer (Rinaldi et al., 2016).

Prof. Sarah Millar (University of Pennsylvania, Philadelphia) discussed the roles for histone deacetylases (HDACs) and their interaction with transcription factors leading to chromatin compaction and transcriptional repression. Following up previous work showing the roles for HDAC1 and HDAC2 in the control of embryonic epidermal development (LeBoeuf et al., 2010), she reported that, in contrast to ubiquitous expression of HDAC1/2 in skin epithelia, genetic deletion of *Hdac3* in embryonic mouse epidermis disrupts stepwise differentiation of the epidermis. These data show that HDAC3 coordinates expression of differentiation proteins and lipids to establish a functional barrier via distinct molecular mechanisms.

Dr. Yuri Schwartz (University of Umea, Sweden) and Dr. Elena Ezhkova (Mount Sinai School of Medicine, New York, NY) presented the data on how Polycomb Group proteins operate as epigenetic repressors essential for control of development and cell differentiation (Schwartz and Pirrotta, 2014). Dr. Schwartz discussed similarities and differences between Polycomb mechanisms in different species and linked them to recently discovered pervasive nontargeted survey of the genome by Polycomb Group proteins (Lee et al., 2015). Dr. Ezhkova reported that the loss of function of core components of the different Polycomb complexes (PRC1 vs. PRC2) can result in different or even opposing biological outcomes, despite their shared genomic targets (Dauber et al., 2016; Perdigoto et al., 2016).

Prof. Jonathan Higgins (Newcastle University, UK) discussed how histone H3T3 phosphorylation regulates protein association and dissociation from chromosomes during mitosis and can recruit "reader" proteins or displace them from chromatin. Future research will aim to generate the first genome-wide maps of mitotic histone phosphorylation and to uncover roles of histone phosphorylation in the decisions to retain bookmarks or release proteins from chromatin. This will help uncover mechanisms for memorizing and reprogramming gene expression during cell division (Wang and Higgins, 2013).

Prof. Bogi Andersen (University of California, Irvine) reported on the role of the transcription factor GRHL3 and epigenetic factors in the control of human epidermal keratinocyte differentiation and migration: during differentiation, GRHL3 primarily binds to superenhancers and activates transcription of epidermal differentiation genes, and during migration, GRHL3 binds to promoter regions and represses the expression of inhibitors of migration (Hopkin et al., 2012; Peyrard-Janvid et al., 2014). These data suggest that alterations in the enhancer structure and spatial rearrangement in chromatin binding of key transcription factors are responsible for the different functional states of keratinocytes.

The 2016 John M. Wood Memorial Lecturer Prof. Elaine Fuchs (Rockefeller University, New York, NY) described her most recent work on the epigenetics and transcriptional regulation of stem cells during tissue regeneration, wound repair, and malignant progression. Her team has unravelled interactions between stem cells and their environment, which are manifested through dynamic changes in chromatin landscapes that orchestrate stem cell plasticity and allow stem cells to survive outside their native niche (reviewed in Adam and Fuchs, 2016; Fuchs, 2016). Prof. Fuchs has also reported about recent insights into the biology of enhancers in skin epithelial stem cells and how pioneer transcription factors regulate superenhancer assembly in normal and malignant keratinocytes (Adam et al., 2015; Yang et al., 2015).

HIGHER-ORDER CHROMATIN REMODELING, THREE-DIMENSIONAL GENOME ORGANIZATION, AND REGULATION OF ENHANCER-PROMOTER INTERACTIONS

Nuclear compartmentalization of the genes, enhancer elements, and transcription machinery play essential roles in the control of gene expression (Bickmore and van Steensel, 2013; Cremer et al., 2015; Dekker and Mirny, 2016). Prof. Peter Fraser (Babraham Institute, Cambridge, UK) reported on the progress in the further development of chromatin conformation capture technology that allows identification of spatial chromatin interactions in the nucleus. Fraser's laboratory developed a promoter-capture Hi-C technology to identify distal sequences interacting with annotated gene promoters in 17 primary human hematopoietic cell types and several mouse cell types. In his talk, Peter Fraser reported that more than half of the identified interactions are cell type- or lineage-specific and preferentially link actively transcribed promoters with distal active enhancers. These population studies provide useful information on the range of genome interactions with exciting insights into human genetic variation and disease (Gilbert and Fraser, 2015).

Drs. Mike Fessing and Andrei Mardaryev (University of Bradford, UK) presented the data on the higher-order chromatin organization of the epidermal differentiation complex locus in keratinocytes (Botchkarev et al., 2012; Fessing, 2014; Fessing et al., 2011; Mardaryev et al., 2014). These talks conclude that spatial interactions within and between lineage-specific gene loci in keratinocytes are essential for coordinated regulation of gene expression, implicating their role in governing epithelial differentiation and function.

Dr. Christina de Guzman Strong (Washington University, St. Louis, MO) identified previously dynamic chromatin remodeling and activation of the epidermal differentiation complex locus with respect to an epidermal-specific enhancer, 923, thus enabling enhancer-centric studies to elucidate transcriptional activation (Oh et al., 2014). Data presented in her talk show that intraepidermal differentiation complex chromatin contacts are enriched with respect to the 923 enhancer and *Flg* promoter and that transchromatin interactions enriched in loci are involved in the control of gene expression and epidermal function.

Dr. Huiqing Jo Zhou (Radboud University, Nijmegen, The Netherlands) reported on epigenome profiling of differentiating human primary epidermal keratinocytes and characterized a catalog of dynamically regulated genes and p63-bound enhancers that