Gathering by the Red Sea highlights links between environment and epigenetics

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The number of conferences on epigenetics has been increasing in the past decade, underscoring the impact of the field on a variety of areas in biology and medicine. However, the mechanistic role of the epigenome in adaptation and inheritance, and how the environment may impinge on epigenetic control, are topics of growing debate. Those themes were the focus of the inaugural international King Abdullah University of Science and Technology (KAUST) Research Conference on Environmental Epigenetics in Saudi Arabia, where more than 100 participants from 19 countries enjoyed vibrant scientific discussions and a pleasant February breeze from the Red Sea.

Held on 12–15 February 2017 at the KAUST campus, the conference aimed to offer an innovative program, reflecting the vision of the recently established KAUST Environmental Epigenetics Research Program (KEEP; https://keep.kaust.edu.sa), in collaboration with the Center of Epigenetics and Metabolism (University of California, Irvine) and the Laboratory of Gene Expression at the Salk Institute. The conference was supported by the Office of Sponsored Research (OSR) and the Biological and Environmental Sciences and Engineering Division, KAUST. The program included sessions on the role of epigenome regulation and architecture in cell identity, adaptation, metabolism, memory, reprogramming and plasticity for tissue regeneration. The range of topics included how germ cells build epigenetic memory to be transferred or erased to the next generation; fish adaptation to climate change in the Red Sea; neurobiology of early life stress and memory of traumatic events; the importance of metabolism in feeding and the ability to maintain and reprogram adult stem cells and tissues; how the knowledge of these mechanisms is instrumental to understand aging and tissue regeneration; and the pathogenesis of immunodeficiency, diabetes and neuromuscular diseases. We summarize below some of the themes discussed at the conference, as we feel those topics will dominate the field of environmental epigenetics in coming years.

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Epigenetic control of cell identity and inheritance

Azim Surani (The Gurdon Institute) opened the conference by discussing the specification and epigenetic programming of the human germline. He summarized his group's work developing *in vitro* models to simulate early development and specification of human primordial germ cells (hPGCs) using human embryonic stem cells (hESCs) and induced pluripotent stem cells (hiPSCs)[1]. Using this system, his lab found unexpectedly divergent regulators of PGC fate between human and mouse, notably SOX17; the results showed that SOX17 and BLIMP1 are necessary and sufficient for the induction of hPGC fate[2]. He shared unpublished data on the molecular basis for the divergent roles of SOX family members in the establishment of different cell fates. The observation that some genomic loci 'escape' epigenetic resetting through the germline sparked a spirited discussion on transgenerational epigenetic inheritance and its impact on human evolution and disease. Important questions, such as the potential role of escapee genes in transgenerational inheritance, may be addressed by genetic modification of the mouse model germline using the CRISPR–Cas9 system.

An open question on epigenetic inheritance relates to specificity at the single-cell level. Nicola Iovino (Max Planck Institute of Immunobiology and Epigenetics, Freiburg) showed how specific histone marks persist in germ cells and regulate early *Drosophila* development. This theme was further developed by Robert Schneider (Institute of Functional Epigenetics, Helmholtz Zentrum Munich), whose group identified factors involved in the memory of cellular state across multiple generations using recently developed methods coupling genetics of single cells and their progeny to epigenome profiling and high-throughput sequencing. Charles Plessy (RIKEN) followed up on the topic by discussing parallel single-cell analysis of the epigenome and the promotome, which dramatically increases the power of correlation studies between cells and within a single cell. These quantitative studies illustrate the specificity and control of epigenetic states at the cellular level, providing avenues to study the dynamics of transcriptional epigenetic memory. It is clear from the reports that new developments in high-throughput tracking, sequencing technologies and manipulation of single cells are on the horizon and will provide deeper insights into epigenetic inheritance of cellular state.

Participants at the KAUST Research Conference on Environmental Epigenetics attend a musical performance at the end of a poster session.

Epigenome in the changing environment and adaptation

One of the central themes at the conference was the use of multi-systems, such as neurons in model animals or desert plants and wild fish in coral reefs, to reveal the mechanistic roles of the epigenome and phenotypic variation in development and adaptation. Johannes Gräff (Swiss Federal Institute of Technology in Lausanne) discussed the role of histone acetylation in long-term traumatic memories. Histone acetylation level has been shown to be positively correlated with memory and learning, whereas reduced levels can cause neurodegeneration. Histone acetylation is regulated by histone deacetylases (HDACs); Gräff summarized his lab's current efforts to understand how small-molecule inhibitors of HDACs may heighten neuroplasticity and therefore help the brain overcome traumatic memory.

Ueli Grossniklaus (University of Zurich) focused on epigenetic variation and adaptation in plants by exploring the natural variation in DNA methylation in *Arabidopsis*[3,4]. Whether such epigenetic variation contributes to adaptation to a changing environment has been unclear, but Grossniklaus presented evidence that epigenetic variation is subject to selection and may contribute to adaptive responses to the environment over generations. A key aspect of plant adaptation is the innate immune response to microbes, which involves activation of the MAP kinase signaling cascade. Heribert Hirt (KAUST) showed that the HDAC HD2B is a substrate of the MAP kinase MPK3 and is involved in the epigenetic reprogramming of defense-gene expression.

Adaptation through epigenetic control extends beyond plants, as shown by Timothy Ravasi and Celia Schunter (KAUST), who shared their research on transgenerational adaptation of tropical fish to rapid anthropogenic changes in ocean temperature and CO_2 levels. Their use of non-model organism and integrated approaches (including *de novo* genomes, transcriptomes, proteomes and DNA methylomes) yielded transgenerational molecular signatures, which allowed them to propose possible epigenetic mechanisms for switching genetic networks that control metabolism and behavior during transgenerational adaptation to climate change[5,6].

Adaptation is also remarkable in superior neuronal functions in mammals, as demonstrated by Emiliana Borrelli (University of California, Irvine). Mice with a genetic ablation of the dopamine D2 receptor specifically in dopaminergic neurons exhibit psychotic behaviors that classically model psychiatric disorders. Notably, the prefrontal cortex of these knockout mice showed downregulation of more than 2,000 genes, which correlated with a robust increase of a repressive epigenetic mark on histone H3. Genes whose human counterparts are associated with psychiatric disorders showed enrichment of this repressive mark at their promoters. These findings may lead to pharmacological interventions for the treatment of psychiatric disorders.

Different levels of organization of genetic information

How genetic information is organized in the nucleus and how chromatin architecture influences development and stem cell differentiation remain fascinating questions. Wouter de Laat (Hubrecht Institute) stressed that most methods for measuring 3D chromatin conformation detect only pairwise contacts and are thus unsuitable for studying simultaneous spatial association of multiple loci. He described a novel methodology, named multi-contact 4C, that uses third-generation long-read single-molecule real-time sequencing technology to detect 4–8 spatial neighbors of a given locus[7]. He also explained that the principle behind chromosomal conformation capture—i.e., selectively capturing and amplifying sequences on the basis of cross-linking of physically proximal chromatin—could be applied to targeted locus amplification (TLA) for cost-effective genetic diagnostics[8]. An example of successful implementation of TLA in the clinic is prenatal diagnosis of cystic fibrosis and thalassemia using fetal DNA isolated from maternal blood. These chromosome capture–based technologies could not only help unravel higher-order chromatin-mediated pathogenic mechanisms but also provide fast, accurate and cost-effective diagnosis of diseases in the future. A different approach to investigate chromatin architecture was used by Maria Pia Cosma (Center for Genomic Regulation Barcelona), who discussed a new model for chromatin fiber organization derived from quantitative super-resolution nanoscopy, revealing the profound differences between stem and differentiated somatic cells[9].

The roles of noncoding RNAs that are associated with nuclear organelles in chromatin architecture and the dynamic states of the epigenome were explored in different talks. Muhammad Shuaib (KAUST) described data showing that while human nuclear RNA interference (RNAi) components interact with active enhancers and promoters in the genome, they also associate with architectural long noncoding RNA (lncRNA) and regulate global gene expression by affecting higher-order chromatin structure. A parallel story involving the RNA helicase DHX9 and the nucleolus-associated lncRNA IGS-rRNA was presented by Raffaella Santoro (University of Zurich), who showed that processing of lncRNA IGS-rRNA into pRNA (a noncoding RNA molecule that is complementary to the rDNA promoter) by DHX9 is crucial for heterochromatin formation and loss of pluripotency during embryonic stem cell differentiation[10].

Wolfgang Fischle (KAUST) presented data providing mechanistic insights into how linker histone incorporation and histone tail modifications regulate the epigenome. His work showed that linker histones generally inhibit modifications of different H3 sites and reduce

H3 tail dynamics in nucleosomes. These findings could shed light on the relationship between the dynamics of linker histone distribution and cellular differentiation.

Cell metabolism, regeneration and reprogramming

The circadian rhythm is an environmental adaptation shared by all life forms. Yet its underlying epigenetic components and links to nutrition and metabolic health have begun to be explored only recently. Paolo Sassone-Corsi (University of California, Irvine) shared his group's recent discovery that the circadian clock controls the circadian epigenome, which regulates metabolic enzymatic activity. He also discussed the plasticity of the body's clock and how the clocks of different tissues may become dysregulated owing to pathological conditions such as cancer and changes in gut microbiome.

On the basis of a report about the role of Ezh1–Polycomb responsive complex 2 (PRC2–Ezh1) in mammalian skeletal muscle adaptation to oxidative stress[11], Seba Nadeef (KAUST) presented findings from a collaborative study between the labs of Valerio Orlando and Paolo Sassone-Corsi, which show that genes encoding components of PRC2 show circadian oscillation in muscle and their interaction with clock genes contribute to adaptation to metabolic stress such as high-fat diet or fasting. The close connection between metabolism and epigenetic processes was also illustrated in a study presented by Axel Imhof (Ludwig-Maximilians University), who showed that the attenuation of an age-dependent increase in lysine acetylation results in lifespan extension in fruit flies[12].

A central feature of epigenetic control is its direct impact on various pathways of cellular reprogramming. Juan Carlos Izpisua Belmonte (The Salk Institute) illustrated links between epigenetic mechanisms and regeneration in a wide range of cellular and animal models. These links include rejuvenation of premature aging in hiPSCs[13], cardiomyocyte regeneration[14] and amelioration of age-associated hallmarks in mice and in human cells in culture[15]. Chiara Lanzuolo (Institute of Cell Biology and Neurobiology CNR, Rome) presented data on the role of nuclear architecture in cell fate choice. In a mouse model of muscular dystrophy (in which the mice lack nuclear lamin A), Lanzuolo's group found defects in the muscle–fat equilibrium due to transdifferentiation of muscular satellite stem cells toward adipogenesis. Observed transcriptional changes might be ascribed to an altered nuclear positioning of Polycomb proteins, which are dependent on intact lamin A[16].

The power of hPSCs to uncover molecular mechanisms of disease and differentiation was also illustrated by other participants. Mo Li (KAUST) described an hiPSC model of Wiskott–Aldrich syndrome that revealed unexpected roles of the Wiskott–Aldrich syndrome protein (WASP) in maintaining the integrity of nuclear bodies and regulating gene expression. Antonio Adamo (KAUST) showed that lysine-specific demethylase LSD1, which regulates the pluripotent state, has a key role during stem cells differentiation toward glucose-sensitive cell types. Finally, Francesco della Valle (Orlando lab, KAUST) presented data obtained in human myogenesis and in a transdifferentiation model for dopaminergic neuronal cell reprogramming, showing an unexpected positive role of regulated somatic retrotransposition of L1 retroelements in cell-type specialization and phenotype variation, possibly via production of lncRNAs.

Concluding remarks

The debate on the role(s) of the epigenome and phenotypic variation in inheritance, development, environmental adaptation, tissue regeneration and aging is wide open. The diverse phenotypic contexts linked to epigenome function discussed at the meeting reiterated the question of whether observed epigenetic changes reflect causal or bystander effects. Therefore, investigation of the fundamental mechanisms that link genome function with the environment and identification of bona fide 'environmental epigenetic sensors', such as chemical modifications, noncoding RNAs and metabolites, remain the highest priorities in the field. The exploration of those mechanisms in diverse biological systems and environments will also shed light on the strategies that different organisms may use to adapt to the changing environment. To reach this goal, further efforts should be directed at the development of new technologies in genomics, metabolomics, imaging and modeling. Such research will benefit from collaborations between investigators with different areas of expertise, as well as open exchange of ideas and data, all of which can be sparked and stimulated during scientific conferences. The KAUST Research Conference on Environmental Epigenetics will be a biannual gathering to discuss these rapidly evolving themes, and we hope that the high-quality interactions among participants in the inaugural meeting will continue in the future.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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