The International Human Epigenome Consortium (IHEC): A Blueprint for Scientific Collaboration and Discovery

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Abstract

The International Human Epigenome Consortium (IHEC) coordinates the generation of a catalogue of high-resolution reference epigenomes of major primary human cell types. The studies now presented (cell.com/XXXXXXX) highlight the coordinated achievements of IHEC teams to gather and interpret comprehensive epigenomic data sets to gain insights in the epigenetic control of cell states relevant for human health and disease.

One of the great mysteries in developmental biology is how the same genome can be read by cellular machinery to generate the plethora of different cell types required for eukaryotic life. As appreciation grew for the central roles of transcriptional and epigenetic mechanisms in specification of cellular fates and functions, researchers around the world encouraged scientific funding agencies to develop an organized and standardized effort to exploit epigenomic assays to shed additional light on this process (Beck, Olek et al. 1999, Jones and Martienssen 2005, American Association for Cancer Research Human Epigenome Task and European Union 2008).

In March 2009, leading scientists and international health research funding agency representatives were invited to a meeting in Bethesda (MD, USA) to gauge the level of interest in an international epigenomics project and to identify potential areas of focus. This meeting, and a subsequent conference in January 2010 in Paris (France) ultimately led to the creation of the International Human Epigenome Consortium (IHEC).

The primary goals of IHEC are to coordinate the production of reference maps of human epigenomes for key cellular states relevant to health and diseases, to facilitate rapid distribution of the data to the research community, and to accelerate translation of this new knowledge to improve human health. A critical component of IHEC goals is to coordinate the development of common bioinformatics standards, data models and analytical tools to organize, integrate and display the epigenomic data generated.

IHEC members all contribute to these primary goals, but they also have individual complementary goals such as developing new and improved ways to monitor or manipulate the epigenome, discovering new epigenomic mechanisms, training the next generation of epigenome researchers, exploring epigenomic features associated with disease states, and translating epigenomic discoveries into improvements to human health. This is in keeping with the larger overarching vision of IHEC, which is to help address fundamental questions in how the genome and environment interact during development and aging, and how the epigenome influences health and disease.

There are many strengths to a consortium model, bringing together research expertise and knowledge from across the world. These include the ability to implement and monitor high quality data and assay standards, maximize coverage of human cells and tissues while avoiding unnecessary duplication. Additionally this model helps harmonize data collection, management and analysis, to facilitate sharing and retrieval across countries, and provides open access to data and results. IHEC provides a mechanism to facilitate communication among members, and provides a forum for coordination with the objective of maximizing efficiency among researchers working to understand, treat, and prevent diseases.

Current full members of IHEC include: AMED CREST/IHEC Team Japan; DLR-PT for BMBF German Epigenome Programme DEEP; CIHR Canadian Epigenetics Environment, and Health Research Consortium (CEEHRC); European Union FP7 BLUEPRINT Project; Hong Kong Epigenomics Project; KNIH Korea Epigenome Project; NHGRI ENCODE; the NIH Roadmap Epigenomics Program; and the Singapore Epigenome Project (http://ihec-epigenomes.org/). In the subsequent sections we overview experimental and computational tools developed by IHEC members and highlight key findings from a collection of recent publications from IHEC members.

Indentifying heterogeneity in epigenomic measurements

Cellular and allelic heterogeneity provides a significant challenge in the interpretation of epigenomic signatures that are typically derived from heterogeneous populations of millions of individual cells. To address this challenge we have developed a series of molecular and computational approaches to deconvolute epigenomic signatures from heterogeneous populations. Three independent strategies are presented to explore the heterogeneity at bivalent domains, a “poised state" marking important developmental genes characterized by an active (histone H3 lysine 4 trimethylation, H3K4me3) and a repressive (H3K27me3) mark on the same histone, and reveal that this combinatory epigenetic signature is both lost and gained at key regulatory genes during development (Hirst 2016, Kinkley, Helmuth et al. 2016, Weiner, Lara-Astiaso et al. 2016). Further these methods define previously undescribed co-occurrence patterns of histone modifications on single nucleosomes and in relationship with enzyme accessibility of chromatin. To access the molecular information within a diversity of interacting cell types

in complex tissues we developed *in silico* deconvolution methods that provide estimates of genomic CpG methylation and gene transcription within complex tissues, including solid tumors (Milosavljevic 2016) and hematological neoplasms (Martín-Subero 2016). Finally, a meta-epigenomic approach that combines low-input and single-cell DNA methylation sequencing gave rise to a comprehensive map of the DNA methylation dynamics of human hematopoietic stem cell differentiation, experimentally and bioinformatically accounting for epigenomic heterogeneity (Farlik 2016).

New computational tools bolster the utility of epigenome data for biology and medicine

As of today, IHEC has generated over 7000 multi-dimensional datasets, which are publicly available through several channels. For specialized analyses, the raw data files containing personally identifiable data can be obtained under the controlled access scheme from dbGaP (NIH) and EGA (EBI). For common analyses not using any personally identifiable information, pre-processed data can be obtained from the unrestricted GEO (NIH) and ArrayExpress (EBI) repositories. To guide new users, IHEC has made a substantial investment into dedicated data access tools. The IHEC Data Portal (http://epigenomesportal.ca/ihec/) provides a comprehensive overview and single point of entry for accessing all IHEC reference epigenome data (Bourque 2016). This portal is complemented by tools for comparing epigenome data between cell types (Valencia 2016), for inferring epigenomic co-localization networks (Juan, Perner et al. 2016), for programmatic data access and filtering (Albrecht, List et al. 2016), for analyzing the results of epigenome-wide association studies (Breeze 2016), for detecting ChIP-seq peaks (Bourque 2016) and for predicting transcription factor binding (Schulz 2016). As part of IHEC's mission to develop quality standards for epigenomic data, we have validated the accuracy of epigenome assays and proposed widely used quality standards for epigenome mapping (http://ihec-epigenomes.org/). In addition, we investigated the effect of sequencing depth on the accuracy of whole genome bisulfite sequencing (Libertini, Heath et al. 2016, Libertini, Heath et al. 2016) and conducted a community-wide benchmarking study comparing locus-specific DNA methylation assays across 18 laboratories in seven different countries, establishing that DNA methylation profiling is accurate and robust enough for use as a clinical biomarker (consortium 2016). Finally, two studies have started to connect epigenome regulation to the 3D structure of the nucleus, using high-resolution imaging (Larabell

2016) as well as computational methods for integrative data analysis (Pancaldi, Carrillo-de-Santa-Pau et al. 2016).

Epigenome analysis identifies pathways involved in cell fate determination and disease

Recent technical advances allow the generation of genome-wide signatures for primary human cell types of increasingly narrowly defined biological properties. This provides new insights into the epigenetic and transcriptional basis of their differentiation capabilities, their responses to specific stimuli, and how these are altered in pathological conditions.

Exciting new information can be retrieved from epigenomic differences between developmentally linked cell types, their inferred relationships, and the likely identity of chromatin and transcriptional regulators of their differentiation and developmental states (Arima and Sasaki 2016, Hirst and Eaves 2016, Polansky 2016, Santana and Spicuglia 2016, Schuyler 2016, Wallner, Schroder et al. 2016). Analysis of cells subjected to specific external stimuli shed new light on how environmental cues alter epigenomic states in both normal and pathological tissues (Arts 2016, Holland, Lowe et al. 2016, Polansky 2016, Stunnenberg 2016). Memory of such external exposures, coordinated at the chromatin level, can influence future behavior of the cell and susceptibility to disease under stress conditions.

Epigenomic profiles of normal cell types also provide a valuable comparator for their counterparts in diseased tissues. Such comparisons have been performed in solid tumors such as breast cancer (Hirst and Eaves 2016) and extra-cranial malignant rhabdoid tumors (Chun, Lim et al. 2016), hematological neoplasms such as mantle cell lymphoma (Martín-Subero 2016) and chronic lymphocytic leukemia (Rendeiro, Schmidl et al. 2016). These analyses have not only provided unprecedented insights into disease pathogenesis but have also enabled the stratification of diseases into novel clinico-biological subtypes. On the one hand, pathological tissues and cells exhibit epigenetic imprints of the developmental or differentiation stages from which they originate and, on the other hand, they acquire disease-specific epigenetic alterations. Exciting outcomes of these comparisons are the identification of disease-specific regulators and distant enhancers regulating oncogenes, the functional characterization of mutated/aberrantly expressed chromatin and transcriptional regulators, and how these might be

profitably targeted by novel (Franci, Sarno et al. 2016) as well as existing therapies (Angela, Carafa et al. 2016, Chun, Lim et al. 2016, Martens 2016).

These insights, together with the understanding of how immune cells alter their epigenomes in reaction to or to contribute to a diseased environment (Pagani 2016, Paul 2016, Santana and Spicuglia 2016, Stunnenberg 2016), and how the epigenomic changes are established by environmental cues (Holland, Lowe et al. 2016), will likely lead to new biomarkers for a better diagnosis and estimation of prognosis, as well as improved epi-drug based treatments and outcomes for a plethora of disease states. A present example of epigenomic analysis that may lead to testable clinical intervention is the reversal of endotoxin-induced tolerance in macrophages(Stunnenberg 2016).

The IHEC consortium is confident that the comprehensive analysis of epigenomes in health and disease will lead to a better understanding of how differentiation and stability of cellular phenotypes is controlled on a molecular level. By identification of novel biomarkers as well as targets for therapy, this will likely lead to improved treatment and outcomes in a variety of diseases.

Epigenetic Marks Illuminate Effects of Noncoding DNA Variants in Disease

A major challenge following the identification of DNA variants associated with different diseases is pinning down their effects, especially when they lie in noncoding regions of the genome. A common mechanistic hypothesis is that the genetic variant affects the function of a cis-regulatory element and thereby the expression of a gene, which then influences the disease phenotype. To confirm such a hypothesis, it is important to characterize the molecular phenotypes that mediate the effect of genotype on disease. The IHEC studies capitalize on epigenomic information to address these questions, and several papers in the package take on the question of DNA variants in disease directly. For example, a study of population variation in epigenetic states and gene expression in three human blood cell types showed that these molecular traits were often influenced by the same genetic variants in a coordinated manner, and underpinned hundreds of previously reported autoimmune disease associations (Soranzo 2016). Moving one step further along the path from genotype to phenotype, a related study catalogued population variation in cellular traits (36 blood-cell parameters) in a cohort of 173,480 individuals, and again detected

correlations with genetic variation (Soranzo 2016). Notably, genetic loci associated with blood cell traits were frequently linked to epigenetic and transcriptomic traits and also to autoimmune conditions, schizophrenia and heart disease, potentially implying an etiological role for blood cell parameters. Along similar lines, correlations between genotype and histone acetylation variation in specific brain regions, termed histone acetylation QTLs (haQTLs), provided candidate regulatory variants at multiple loci associated with psychiatric diseases (Prabhakar 2016).

The three-dimensional structure of chromosomes within the nucleus constitutes a key layer of epigenetic information, since it can generate diverse readouts from a constant genome sequence. From a practical standpoint, one can use maps of long-range loops between enhancers and promoters to determine which gene is regulated by a disease-associated noncoding variant. For example, maps of long-range contacts in 17 primary human blood cell types exhibited systemic variation across cell types and identified over 2,500 potential disease genes when combined with a database of disease-associated variants (Fraser 2016). Similarly, chromatin contact maps in 21 primary human tissues and cell types yielded a large compendium of candidate genes when combined with known disease-associated noncoding variants, and also revealed thousands of Frequently Interacting REgions (FIREs) with unusually high levels of long-range chromatin contacts (Ren 2016). Together, the studies in this section play a crucial role in using epigenetics to fill in the gaps between genotype and disease phenotype.

Further Exploration

A challenge faced by international consortia working with human data is the need to efficiently and openly share their data while sufficiently protecting the identity of participant donors from potential re-identification. The response of the community has been to develop a “controlled access” governance framework to provide an additional level of privacy and security protection to the sharing of sensitive data. Our commentary (Joly 2016) presents the advantages and limitations, associated with controlled access, and introduces other, less demanding, data protection and security models including registered access, open consent and privacy enhancing technologies. Following a critical review of each of these alternative models, we conclude that, while all present specific advantages, none of them is currently ready to replace “controlled access”. However, as we become more familiar with data sharing, including

its risks and benefits, it is hoped that the amount of procedural scrutiny around data sharing can be simplified. In this context the lighter protection and security models we describe here will take growing importance for data intensive health research.

IHEC Looking Forward

Epigenomic assays have revealed that selected subsets of regulatory elements in our genomic blueprints are read differently by gene expression machinery to maintain expression of the suites of genes needed for cellular functions. Genome-wide epigenomic data for a diverse set of human cells and tissues also have great utility for generating hypotheses about the regulatory elements associated with complex human diseases. These hypotheses can be tested by disease experts in the broad scientific community, for instance using CRISPR-based profiles to function (P2F) approaches for epigenome editing and screening (Beck 2016).

Although IHEC is well on its way towards accomplishing its primary goals of generating high quality reference epigenomes and making them available to the scientific community, much more remains to be done. As IHEC itself further develops, we anticipate shifting our focus towards a number of possible new directions. These include extensions of the previous goals as well as new opportunities to drive towards the overarching vision of improving human health including the integration of information from the environment and aging in the interpretation of cellular states. Advances in technology will allow investigation of epigenomic changes in single cells rather than populations and the characterization of tissue/disease-linked heterogeneity. Understanding natural and disease-linked variation in human epigenomes has already begun through IHEC, and will be expanded upon. Targeted editing of the epigenome to functionally validate regulatory mechanisms, has been gaining interest. Deeper investigation of epigenomic changes during critical developmental periods and upon environmental exposure are natural extensions of current work. Integration of epigenomic and other –OMIC approaches (such as proteomics, metabolomics, transcriptomics and analyses of the microbiome) is already underway in several countries. In particular, there is considerable interest in integrating epigenomic, transcription factor binding, and expression data with chromatin conformation and sub-nuclear imaging

information to develop a unified understanding of the 3D organization and regulatory dynamics of the nucleus. There have been considerable new and exciting insights in the fields of cancer and inflammation in recent years, revealing primary epigenomic alterations associated with disease pathology. A key interest moving forward is to translate the knowledge gained through basic epigenomic investigations and resource generating consortia such as the IHEC to improve disease diagnosis, stratification and treatment through the continued development of epigenomic-based biomarkers and small molecule epigenetic therapeutics. These could be investigated in longitudinal and well-controlled intervention studies of epigenomics in relation to disease, aging, and environmental exposure.

While not an exhaustive list, the above directions illustrate the wide range of potential opportunities provided by a coordinated, comprehensive assessment of epigenomic function. Future directions of the IHEC consortium will depend on the specific interests of the member projects, and an ongoing assessment of the best areas to continue to add value in epigenomic investigations.

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