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Comparative epigenomics: defining and utilizing epigenomic variations across species, time-course, and individuals

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Abstract

Epigenomic profiling, by revealing genome-wide distributions of epigenetic modifications, generated a large amount of structural information about the chromosomes. Epigenomic analysis has quickly become a big data science, posing tremendous challenges on its translation into knowledge. To meet this challenge, comparative analysis of epigenomes, dubbed *comparative epigenomics*, has emerged as an active research area. Here, we summarize the recent developments in comparative epigenomic analyses into three major directions, namely the comparisons across species, the time-course of a biological process, and individuals. We review the main ideas, methods, and findings in each direction, and discuss the implications to understanding the regulatory functions of the genomes.

Epigenomes play pivotal roles in cell identity, organismal development and disease processes [1, 2], contribute to regulating cognition and behavior [3] and reflect personal variation [4]. By integrating environmental signals with genomic instructions, epigenomes are instrumental in bridging genotypic variation and phenotypic diversity. The rapid growth of high throughput sequencing has substantially reduced the costs of mapping epigenomes. A few new common understandings have been established through epigenomic profiling. First, each cell type possesses characteristic chromatin states [5-8]. Second, cis regulatory elements possess specific chromatin signatures, characterized by combinations of epigenomic marks [9-11]. Third, a large class of new genes that produce long intergenic non-coding RNAs (lincRNAs) possess similar epigenomic characteristics to coding genes, and thus can be identified and annotated in the genome [12, 13].

Epigenomic analysis has quickly become a big data science, posing tremendous challenges on its translation into knowledge. One dimension of the humongous growth of epigenomic data is in size, which is powered by three orthogonal engines. First, high-throughput sequencing enabled

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gigantic scales of data generation. Second, the enhanced data federation merged data across multiple labs and multiple institutions. Third, the raw data were transformed into processed data by analysis software, which becomes a multiplier of the (raw) big data. A second dimension of the growth of epigenomic data is in complexity and heterogeneity, which is at least partially by multi-dimensional data reflecting different aspects of the epigenetic states, including but not limited to protein-DNA interactions, histone and DNA modifications, long-range interactions, RNA-chromatin interactions, and the increasingly popular time-course experimental design.

The challenge of translating epigenomic data into the knowledge of regulatory functions of the genome has been met by the recently developed “comparative epigenomics” approach [14-17]. Comparative analysis is perhaps the oldest and the most essential approach to study biology. The soon that epigenomic maps were produced in a genome-wide manner, comparative analysis between cell types were started with embryonic stem cells and adult cell types [8, 18, 19]. Such comparisons led to the early discovery that embryonic stem cells possess a specific combination of epigenomic marks, dubbed bivalent domains [20]. This intuitive cell type comparison provided early insights but did not fully reveal the information buried in epigenomic data. Since then, new comparison methods have been explored and a few breakthroughs were made in the recent years.

The three dimensions of epigenomic comparisons

Epigenomic comparisons have been carried out between species, between time points of biological processes, and between individuals of a population. Each of the three dimensions of comparisons provided unique insights to the roles of the epigenome in modulating physiological outcomes and the mechanisms of forming the epigenomic modifications (Figure 1).

Cross-species epigenome comparisons

Cross-species comparisons of genomic sequences identified conserved and human-specific genomic elements, among which a subset showed conserved and human-specific functions [21, 22]. By contrast, it was not clear what insights could cross-species epigenome comparisons provide until recently [15, 23, 24]. A central question was whether epigenomic comparisons could increase our capacity of interpreting genomic functions. Two early works mapped DNA methylation in eight diverse plant and animal genomes and revealed the shared and species-specific features of DNA methylation [25, 26]. Histone modifications and transcription factor (TF) binding were also mapped and compared [27]. A comparison of adipose differentiation processes between humans and mice revealed a similarity of chromatin marks near the orthologous genes with similar expression patterns. However, the majority of open chromatin marks and TF binding sites were not shared between the two species, suggesting divergent genetic functions of the orthologous genomic regions in a comparable biological process [27]. These data may contribute to future studies of evolutionary turnover of TF binding sites and evolutionary changes of transcription networks [28] .

Cross-species epigenome comparison faces two fundamental challenges. The first is the lack of fundamental understanding of how epigenomes evolve. We do not know the expected

variation of the epigenomes without selection pressures to serve as the control for defining "conserved" or "changed" epigenomic signatures. Second, a concrete deliverable or a killer application of such analyses must be identified. Xiao et al. set off to explore the basic evolutionary properties of the epigenome in the contexts of both genomic and transcriptomic evolution using pluripotent stem cells of the humans, mice, and pigs [15]. A correlation between the interspecies changes of the epigenomic modifications and the expression levels of the nearby genes was observed in a genome-wide analysis of all the known orthologous genes. However, interspecies changes of the promoter sequences did not exhibit a positive correlation with the interspecies gene expression changes in a genome-wide analysis [15]. In terms of the co-evolution of the genomic sequence and the epigenomic marks, the conservation of H3K27me3, H3K4me3, H3K36me3, H3K27ac, and 5-mC were correlated with sequence conservation, whereas the conservation of H3K9me3, H3K4me1, H3K4me2, and H2A.Z did not exhibit a positive correlation with genomic conservation. In summary, the genome and the epigenome exhibited correlated changes, so did the epigenome and the transcriptome, however the genome and the transcriptome did not exhibit detectable correlated changes at the whole genome scale (Figure 2).

Based on the observation that some co-localized pairs of epigenomic marks tend to exhibit stronger conservation signals, Shu et al. posited that the conserved co-localization of different epigenomic marks can be used to discover regulatory sequences (Figure 3). They experimentally validated all the seven pairs of epigenomic marks identified by this approach. This exercise proved for principal that comparative epigenomics could reveal the regulatory features of the genome that cannot be discerned from sequence comparisons alone [21].

Comparative epigenomics did not only reveal conserved regulatory features, but could identify human-specific enhancers and promoters. Cotney et al. compared H3K27ac maps in the embryonic limbs at comparable developmental stages in humans, rhesus monkeys, and mice [17]. A total of 302 genes exhibited greater expression and enhanced H3K27ac in their genomic neighborhoods in humans. Some of the putative enhancers with human-specific gains of H3K27ac signals overlapped with the genomic sequences with accelerated changes in the human lineage, corroborating with the idea that these genomic regions were not evolved into regulatory sequences until recently.

Time-course epigenome comparisons

Epigenomic modifications change during developmental processes, and some of the epigenomic changes are associated with gene expression changes [15, 16]. Thus, the epigenome adds a dynamic layer of regulatory information onto the genomic sequence and enables a genome to dynamically orchestrate gene expression in different cell types [17, 18]. It is conceivable that if epigenomic maps were obtained at multiple time points during a developmental or differentiation process, they can be utilized to identify the genomic (cis-) regulatory sequences specific to this process.

Earlier works directly compared across different cell types, and found characteristic epigenomic marks or their combinations in different genomic features, such as promoters and gene bodies [7, 8, 29, 30]. Cell type specific regulatory sequences were also identified,

which were often required for the development or maintenance of that cell type [29, 30]. Using the correlations between the epigenome, the transcriptome, and the TF binding sites across cell types, two groups assigned enhancers to putative target genes and predicted cell type specific enhancers [7, 31, 32].

Mapping and comparing epigenomes during a developmental or a differentiation process has become a popular experimental approach. The overriding tenet of these experiments was to reveal the regulatory mechanisms that govern the decision making in these developmental or differentiation processes [15, 33-37]. Three types of information were obtained. The first was the locations of the regulatory sequences specific to each progress. The second was the time series of activation or repression events mediated by these regulatory sequences. The third was the unexpected associations of different epigenomic marks, which co-localize to the same genomic regions at the same time.

The unexpected co-localization of different epigenomic marks at the same developmental time may reveal their combinatorial functions. H3K36me3 and H3K4me1 co-localized in undifferentiated embryonic stem (ES) cells and likely marked active enhancers [15]. H2A.Z and H3K4me3 likely marked poised promoters in ES cells [15], whereas H2A.Z and H3K4me1 marked active enhancers during hematopoiesis [33], indicating multi-faced roles of H2A.Z. Besides, the co-localization of DNA methylation (5-mC) and H3K4me1 was evident at putative distal regulatory elements in undifferentiated human ES cells [37]. Interestingly, 5-mC and H3K4me1 did not tend to co-localize in mouse ES cells (Figure 2A of [15]), and CpG sites were under strong selection in the humans [15]. These data invite the question that whether 5-mC is associated with human specific enhancer activities.

Although developmental studies have so far dominated the published time-course epigenomic analyses, analyses of normal, ageing, and disease processes in adults are catching up. A circadian analysis of the liver epigenome revealed that the robust transcript oscillations often correlated with rhythmic histone modifications in promoters, gene bodies, or enhancers [38]. Histone modification levels in monkey brains were correlated with their ages [11]; and perhaps most strikingly, DNA methylation levels at a defined set of genomic locations were strongly predictive of human ageing in all analyzed cell types and tissues [39, 40]. These data provide a foundation for removing the age effect from the future analyses of disease epigenomes.

The increasing number of temporal epigenomic studies posed a strong demand of analysis tools. Yu et al. developed a probabilistic model to cluster genomic regions by the similarities of their temporal epigenomic patterns [41]. This model assumes that there is a finite number of types of genomic regions, and each type possess a characteristic temporal epigenomic pattern, exemplified by the changes of each epigenomic mark. This assumption was translated into a finite mixture of hidden Markov models (HMM), where each component of the mixture is an HMM that generates the instances of the observed temporal patterns. Applying it to a differentiation process, this model not only clearly distinguished gene bodies, promoters, and enhancers, but also predicted bidirectional promoters, miRNA promotes, and piRNAs with high accuracies. In addition, several rules on the effects of combinatorial epigenomic changes on mRNA expression and non-coding RNA (ncRNA)

expression were derived, including a simple rule governing the relationship between 5-hmC and gene expression levels. Two endoderm specific enhancers were identified, which led to the characterization of a positive feedback loop between endoderm TFs Sox17 and FoxA2. Thus, temporal epigenomic analyses could reveal a fraction of the transcription networks of the biological process of interest.

Comparisons between human individuals

One of the central questions of biology is the causal relationship between molecular and phenotypic variations between individuals. Genome-wide association studies (GWAS) are among the initial steps towards addressing this question [42]. Overall, the GWAS studies on many different diseases and phenotypic groups have amounted to two major lessons. First, there are genomic loci and specific DNA sequences in those loci that are associated with diverse human traits, including both physical and behavioral traits. Second, a relatively small percentage of the variation of a trait can be accounted for by genomic variation alone, for example, about 10% of height variation in humans [43]. These lessons prompted the searches for other molecular variations that may explain personal differences, and the epigenome became a natural candidate for these investigations.

The involvement of epigenomes to the analyses of personal variation invoked two types of questions. First, taking the epigenomes as the molecular signatures, how do they correlate with phenotypic variation? Second, taking an epigenome as a molecular phenotype, what genotypes are responsible for such a phenotype? The experimental design and analytical method for addressing the first question are typically case-control studies for identification of differentially epigenetically modified regions. DNA methylation (5-mC) was the first epigenomic mark analyzed for such a purpose, and both hyper and hypo methylation sites were found in specific genomic regions in cancer [44], type I diabetes [45], and psychosis [46]. Not only diseases but also age difference [39] and environmental differences could result in differential methylation on specific CpG sites in the genome [47]. The comparison of monozygotic twins is a special control-case design, which leveraged the matched genomes for parsing out the environmental contribution to personal epigenomic variations [48].

The next key question is to what extent genomic variations determine epigenomic variations. Both local and distal genomic sequences could contribute to the epigenomic variation of a specific chromosomal region. Epigenome-wide association studies (EWASs) were proposed to narrow down the genomic regions responsible for an epigenomic variation [49]. The power of EWAS mapping could be enhanced by accounting for potential confounding factors such as cell type differences [50]. The power could be further enhanced by considering the allele differences of epigenomic modifications, which essentially increased the sample size of an experiment [51]. Besides 5-mC variation, the variation of histone posttranslational modifications caught recent attentions [52-54]. Both the local genomic sequences and the local TF binding contributed to explain histone modification variations. These data substantiate the idea that the DNA sequence controls epigenomic modifications.

In summary, inter-individual comparisons of the epigenomes provided the evidences that both nature (the genome) and nurture (the environment) modulated epigenomic phenotypes. The major evidences of the genomic contribution came from the correlation of genomic and epigenomic changes across individuals, whereas the role of nurture was clearly manifested in the epigenomic differences of monozygotic twins.

Looking forward, because TF binding is a major driver of many cellular processes, it would be ideal to predict TF binding intensities in any region of a personal genome. Furthermore, because the technologies for mapping epigenomes have become increasingly accessible, it would be useful to take both the genomic sequence and the epigenome into account for predicting (personal) TF binding. A thermodynamic model called APEG (Affinity Prediction by Epigenome and Genome)has been developed to address these needs [55]. When appropriate data become available, this model may assist to investigate a number of open questions. First, how do epigenetic modifications quantitatively modulate the binding affinity of a TF to a given DNA sequence? Second, whether the influence of the local epigenome on TF-DNA binding sensitive to the local DNA sequence? Third, many TFs have preferred DNA recognition motifs; are there TF-specific epigenomic recognition codes? Fourth, how the epigenome regulates the variability of gene expression among genetically identical cells ? Finally, how does the epigenome modulate the personal variation of TF-binding? So far, these questions have only being addressed in theory or at an extremely limited scale [55].

Analysis and visualization tools for comparative epigenomics

A set of tools are particular useful for comparative epigenomic analyses (Table 1). ChromHMM utilizes epigenomic data from multiple cell types to infer shared and cell type specific chromatin states [56]. GATE (Genomic Annotation using Temporal Epigenomic data) is designed for modeling and comparing temporal changes of the epigenomes [41]. UCSC Genome Browser can visualize epigenomic datasets from multiple individuals [57]. CEpBrowser (Comparative Epigenome Browser) is a powerful visualization tool for comparing epigenomic patterns across species [58]. It is also a convenient tool for interacting with stem cell epigenomic datasets [15] and ENCODE datasets [6, 31]. APEG (Affinity Prediction by Epigenome and Genome) can predict TF-DNA binding affinity using personal genome sequence and epigenomic data [55].

Conclusion

Epigenomic analysis has quickly become a big data science, posing tremendous challenges on its translation into knowledge. The challenge of translating epigenomic data into the knowledge of regulatory functions of the genome has been met by the recently developed “comparative epigenomics” approach. Epigenomic comparisons have been carried out between species, between time points of biological processes, and between individuals. Each of the three dimensions of comparisons provided unique insights to the roles of the epigenome in modulating physiological outcomes and the underlying mechanisms of forming the epigenomic modifications.

The epigenome encompasses not only the epigenetic modifications but also other features such as DNA looping and RNA-chromatin interactions. It is foreseeable that more data of these types will be generated across species, individuals, or time points, thus allowing for comparative studies. It can be useful to speculate the experimental designs and analytical methods that may reveal the mechanisms and the physiological impacts of these epigenomic interactions.

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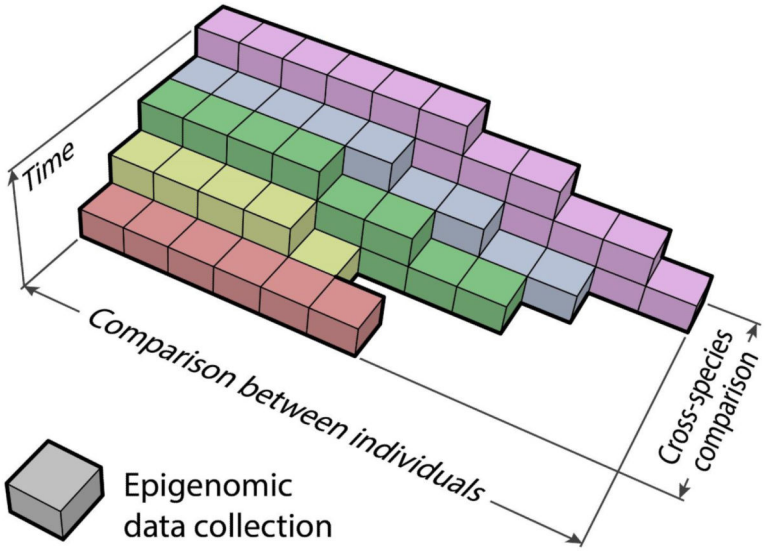

Figure 1.
Dimensions of epigenomic comparisons. Each cube represents an epigenomic dataset.

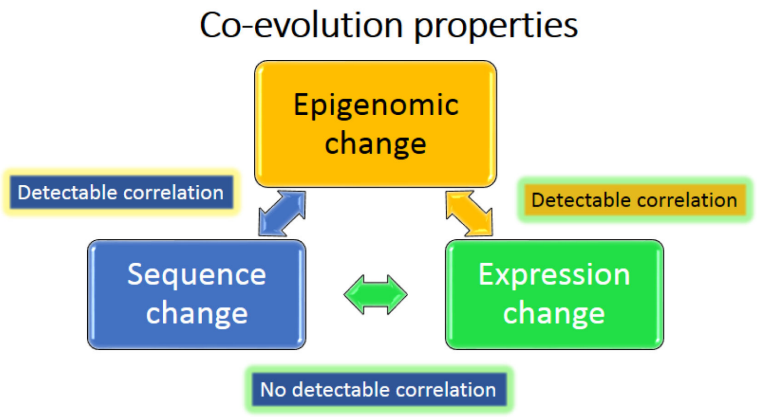

Figure 2.
The inferred co-evolution properties of the genome, the epigenome, and the transcriptome by Xiao et al.

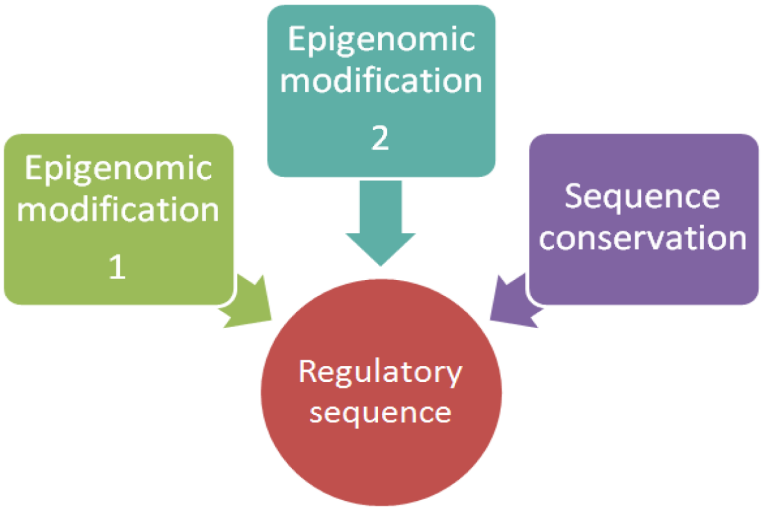

Figure 3.
Using epigenomic conservation together with genomic conservation for annotating regulatory sequences.

Table 1

Analysis tools for epigenomic comparisons.

Tool	Data type	Utility	Ref.
Segway/Segtools	ChIP-seq, MeDIP-seq	Bird's-eye view of complex genomic data sets, identifying recurring patterns.	[59]
Spark	Any NGS data	Interactive pattern discovery	[60]
ChromHMM	ChIP-seq	Classify functional genomic regions	[56]
GATE	ChIP-seq, RNA-seq	Time-course modeling and comparison	[41]
UCSC Genome Browser	ChIP-seq, RNA-seq, other NGS data	Epigenomic visualization combined with comparative genomics	[57]
CEpBrowser	ChIP-seq, RNA-seq	Interspecies comparison and visualization	[58]
APEG	ChIP-seq, personal genome	Predicting TF binding based on personal genome and/or epgienome	[55]