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Introduction

The European Commission network of excellence “EpiGeneSys” has been in operation since 2010 and the third annual meeting took place at the Babraham Institute in Cambridge from 4th to 6th December 2013. EpiGeneSys is an ambitious project studying epigenetics with an emphasis on systems biology. The marriage of these two disciplines is desirable because systems biology approaches are essentially designed to make sense of biological systems that are highly dynamic and involve a plethora of components, both of which are features of epigenetics.

In addition to the 22 permanent members of EpiGeneSys, there are 20 RISE1 (research integrating epigenetics and systems biology) members, who are early career stage researchers, and 97 associates. The meeting in Babraham gave this illustrious group of scientists and their lab members the opportunity to come together for a few days of excellent talks and discussions to catch up on the scienti c highlights of the network, as well as the network’s other functions such as training, career development and public engagement.

The research of EpiGeneSys is divided into four main areas covering dynamics of epigenetic regulators, the relationship between genotype and epigenotype, the in uences of environment and nutrition on the epigenome and nally, building an integrated computational epigenetics framework. At the Babraham meeting there were highlights from all of these areas, and in this report we present a selection to illustrate key issues under discussion and to indicate the future trajectory of EpiGeneSys research.

Genotype to epigenotype

out the genome, altered regulation of transposable elements and impaired cell proliferation. Levels of HMR and LHR are different between the two Drosophila species, which may have arisen as a response to species-speci c changes in the abundance of transposable elements that occurred during divergent evolution.

The relationship between genetics and epigenetics is not all one-way

previously used computational classi - cation strategies to interrogate combinations of proteins and epigenetic marks, and reported that ve major types of chromatin can be distinguished in Drosophila cells. New data presented at the meeting showed that the same ve chromatin types are also observed in human K562 cells, revealing that many common features at the genome-wide level are conserved between Drosophila and human cells. Filion extended these studies by performing the same analysis for human embryonic stem cells (ESC), and although broadly similar, several interesting differences were observed. “Black” chromatin, for example, which is characterised by the absence of DNA binding factors, is detected with a similar abundance between K562 and ESC, ” [(ct4T.6(c.5(5 oen)-l5e .7o8T(studi8189(D 4(facc.5(5 oen)-l5(thC,)5329(Dus2 genetic changes depending on genome

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position. Gael Yvert (CNRS, Lyon, France) described experiments comparing histone acetylation patterns in three different yeast strains. Nucleosome positions and acetylation patterns varied in complex ways; sites with conserved nucleosome positioning and conserved acetylation were observed, but sites showing conservation of neither or only one of these properties were also readily detected. To elucidate genetic and epigenetic contributions to this heterogeneity, histone acetylation was stripped by drug treatment and then allowed to re-establish over a number of generations. Quantitative differences in levels of histone modi - cations were found to be either “labile” or “persistent” depending on whether they were re-established or not after drug treatment. Remarkably, “persistent” variations correlated well with those linked to genetic determinants whereas “labile” variations did not, showing clear contributions of both genetic and epigenetic information to intra-species variation of the histone modi cations landscape [4].

The in uence of the genome on the epigenome is of more than theoretical importance. Cihangir Yandim (Imperial College London, UK) reported the results of a study on the autosomal recessive disorder Friedreich’s Ataxia, which is caused by an expansion of GAA triplet repeats in an intron of the FXN gene. The expanded triplet repeat tract seeds an aberrant region of heterochromatin, which spreads bidirectionally, leading to transcriptional silencing of the FXN gene. Importantly, heterochromatinisation could be inhibited using the histone deacetylase inhibitor nicotinamide. Administration of nicotinamide to a cohort of Friedreich’s Ataxia patients in a Phase II clinical trial led to a signi cant increase in FXN mRNA and protein levels, proving the concept that drugs targeting epigenetics can have clinical applications [5].

New insights into dosage regulation

Dosage compensation in various species has long provided a paradigm for epigenetic regulation of gene expression. Asifa Akhtar (Max Planck Institute of Immunobiology and Epigenetics, Freiburg, Germany) showed that two related MOF-containing complexes, MSL and NSL, can control dosage compensation in mouse ESC, but achieve it through two distinct pathways [6]. MSL binds the two active X-chromosomes in female ESC and reinforces Tsix transcription, thereby limiting Xist expression. In contrast, NSL positively regulates pluripotency factors, including Oct4 and Sox2, in turn leading to suppression of Xist expression. These ndings reinforce the concept that multiple mechanisms are used to ensure correct dosage regulation during development.

Caroline Dean (John Innes Centre, Norwich, UK) addressed how environmental signals can in uence gene expression and phenotype. An interesting epigenetic system allows environmental signals perceived at one stage to be “remembered” until later in development. Vernalisation, the promotion of owering by cold, involves gradual PcG-mediated epigenetic silencing of oral repressor FLC in Arabidopsis thaliana. But the important question now addressed by the Dean group is how this process is reset every generation? They screened for mutants impaired in the epigenetic reprogramming of FLC. In one hypomorphic mutant, FLC is switched on, but fails to reach wild-type levels. The mutated gene was identi ed as Elf6, encoding a jumonji C domain protein likely to be an H3K27me2/3 demethylase. H3K27me3 levels remain elevated in mutant seeds, therefore demethylase activity is required to erase H3K27me3 in the resetting between generations [7].

The role of non-coding RNAs in genome function

Numerous studies have shown that epigenetic marks can be deposited by non-protein coding RNAs (ncRNAs), particularly those involved in transcriptional repression and heterochromatin formation. This has been well studied at ssion yeast centromeres, where ncRNAs from the outer centromeric repeats are processed by the RNA interference (RNAi) machinery to form siRNAs. These siRNAs direct the formation of centromeric heterochromatin, but the connection between the RNAi machinery and the chromatin modifying enzymes only became clear with the recent discovery of the connector protein Stc1. Elizabeth Bayne (Institute of Cell Biology, Edinburgh, UK) reported a structural analysis of Stc1, showing that the zinc nger domain interacts directly with Argonaute while the C-terminal interacts with the CLRC silencing complex, providing the molecular basis of the connection between RNAi and

Epigenomics in single cells

Single cell sequencing approaches have the potential to revolutionise epigenetics. Heather Lee (Babraham Institute) revealed that even apparently homogenous ESC cultures in fact show distinct epigenetic heterogeneity. However, some cell populations are indeed highly homogenous; Sebastien Smallwood (Babraham Institute) presented the first genome-wide methylomes from single cells, in this case from oocytes, which showed very little sample-to-sample variability providing an

be an active area of future work for members of EpiGeneSys.

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