Preface

What an exciting time in biology we find ourselves in. Many complex genomes are deciphered (Lander *et al.*, 2001; Mouse Genome Sequencing Consortium *et al.*, 2002), leaps and bounds are being made in stem cell biology (Takahashi *et al.*, 2007; Takahashi and Yamanaka, 2006; Thomson *et al.*, 1998), and molecular tools are being refined for precise editing and engineering of DNA (Carroll, 2011; Joung and Sander, 2013; Mali *et al.*, 2013). On top of all this, our understanding and appreciation for epigenetics has made phenomenal advances since the term 'epigenetics' was first put forward by Waddington in the 1940s to unite the fields of genetics and developmental biology (Waddington, 1942). Initially relating to developmental programming, today the designation of epigenetics is more focused and can be defined as the study of the mitotic and/or meiotic heritability of gene expression triggered through a transient initiating event that occurs in the absence of change to the DNA sequence (Berger *et al.*, 2009; Felsenfeld, 2014; Russo *et al.*, 1996).

Despite the many advances, there is so much more yet to be learned about this complex, yet fascinating topic. For example, as illustrated in Fig. 1, who directs and initiates whom? DNA methylation or histone modifications? What about the role of RNA, or DNA structural forms? In my opinion, we are but at the base of the mountain and have an exciting and long adventure of discovery as we clamber ahead.

This book begins with several chapters that focus on epigenetic processes. We start with a discussion of the multifunctional zinc finger protein YY1 (Chapter 1) that performs numerous central roles in epigenetic phenomena.

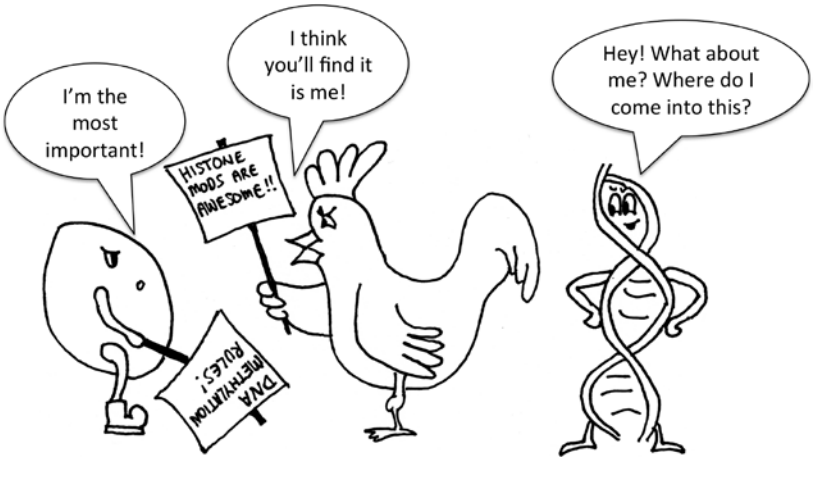

Figure 1 What is the epigenetic hierarchy? Which comes first, DNA methylation or histone modifications? Or is it RNA or the act of transcription, and what role does the DNA have in setting up the epigenome?

Next we transition to two chapters that relate to histone-modifying enzymes. The first focuses on the versatile role of the histone methyltransferase protein SETDB1 in establishing and maintaining gene silencing (Chapter 2), whereas the second discusses the multifaceted role of sirtuins in fungal biology (Chapter 3). The next chapter discusses the distribution and detection of the DNA modification, 5-hydroxymethylcytosine in the genome, and how this relates to development (Chapter 4). After this chapter, various approaches to identify proteins involved in epigenetic processes are discussed, including the remarkable power of an *N*-ethyl-*N*-nitrosourea mutagenesis screen to generate mouse lines with mutations in epigenetic factors that enhance or suppress variegated transgene expression (Chapter 5). This is followed by a chapter that focuses on the global response of chromatin in response to stimuli (Chapter 6), before a discussion of the complex nature of chromatin and epigenetics in defining the centromere of eukaryotic chromosomes (Chapter 7). The next chapter is a broad discussion of dosage compensation with a particular focus on what is known in frogs and toads and why these animals make ideal models to further investigate this process (Chapter 8). The first part of the book is rounded off with a discussion of long non-coding RNAs in epigenetic processes (Chapter 9).

The next section of the book highlights two human genetic disorders that are directly impacted by epigenetics. The first provides an in depth and current review of the autism spectrum disorder Rett syndrome, which is caused by mutations in the methyl-DNA binding protein MECP2, whose gene is located on the X-chromosome and the disease is therefore also impacted by the mammalian dosage compensation pathway, X-chromosome inactivation (Chapter 10). The second disease focused chapter provides and in depth look at the progressive muscle degenerative disorder facioscapulohumeral muscular dystrophy, a complex disease that is impacted by many epigenetic influences (Chapter 11).

Finally, the last section of the book focuses on relatively new aspects of epigenetics. We start with a discussion of challenges and approaches to reprogramming the epigenome (Chapter 12), followed by a discussion of the potential for G4 quadruplex structures as a means for epigenetic inheritance (Chapter 13). The book is then rounded off with four chapters that address current topics in epigenetics. The first discusses the application of epigenetics in cancer diagnosis, prognosis and therapy (Chapter 14). The second (Chapter 15) focuses on transgenerational inheritance: inheritance of phenotype in the absence of exposure (Fig. 2). The third discusses the influence of metabolites on the epigenome (Chapter 16), and the final chapter (Chapter 17) discusses the impact of the environment on our epigenome, an area of growing concern (Fig. 3).

I would like to thank all the contributors for their time and effort in making this book happen, and hope that you, the readers, will enjoy and be as enlightened as I was in its preparation.

Dr Brian P. Chadwick

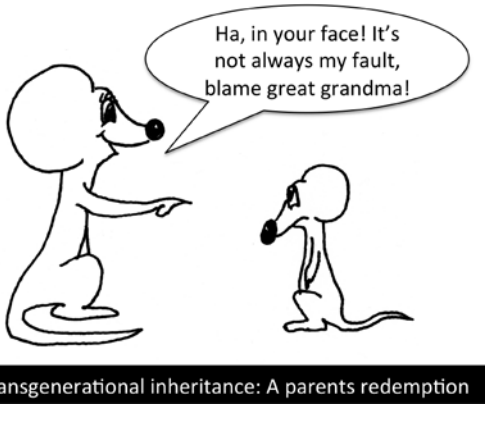

Figure 2 Can we now blame (at least in part) our great grandmother or our grandfather for epimutations that impact us? What are we doing, unbeknownst to us, that will impact our lineage several generations removed?

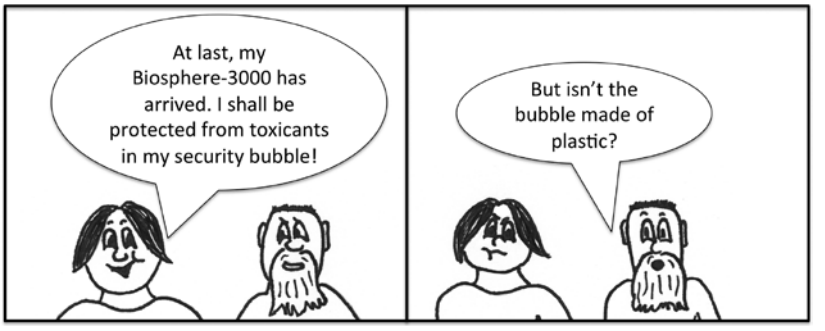

Figure 3 We now know how some environmental toxicants impact our epigenome and increase susceptibility to disease. However, what about those natural or man-made agents that are not currently on our radar?

References

Berger, S.L., Kouzarides, T., Shiekhattar, R., and Shilatifard, A. (2009). An operational definition of epigenetics. Genes Dev. *23*, 781–783.

Carroll, D. (2011). Genome engineering with zinc-finger nucleases. Genetics *188*, 773–782.

Felsenfeld, G. (2014). A brief history of epigenetics. Cold Spring Harb. Perspect. Biol. *6*, 1–10.

Joung, J.K., and Sander, J.D. (2013). TALENs: a widely applicable technology for targeted genome editing. Nat. Rev. Mol. Cell. Biol. *14*, 49–55.

Lander, E.S., Linton, L.M., Birren, B., Nusbaum, C., Zody, M.C., Baldwin, J., Devon, K., Dewar, K., Doyle, M., FitzHugh, W., et al. (2001). Initial sequencing and analysis of the human genome. Nature *409*, 860–921.

Mali, P., Esvelt, K.M., and Church, G.M. (2013). Cas9 as a versatile tool for engineering biology. Nat. Methods *10*, 957–963.

Mouse Genome Sequencing Consortium, Waterston, R.H., Lindblad-Toh, K., Birney, E., Rogers, J., Abril, J.F., Agarwal, P., Agarwala, R., Ainscough, R., Alexandersson, M., et al. (2002). Initial sequencing and comparative analysis of the mouse genome. Nature *420*, 520–562.

Russo, V.E.A., Martienssen, R.A., and Riggs, A.D. (1996). Epigenetic mechanisms of gene regulation (Cold Spring Harbor Laboratory Press, Plainview, NY. USA).

Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., Tomoda, K., and Yamanaka, S. (2007). Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell *131*, 861–872.

Takahashi, K., and Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell *126*, 663–676.

Thomson, J.A., Itskovitz-Eldor, J., Shapiro, S.S., Waknitz, M.A., Swiergiel, J.J., Marshall, V.S., and Jones, J.M. (1998). Embryonic stem cell lines derived from human blastocysts. Science *282*, 1145–1147.

Waddington, C.H. (1942). The epigenotype. Endeavour *1*, 18–20.