3 DEFINING EPIGENETICS

A common thread connecting diverse eukaryotic organisms with respect to fundamental epigenetic principles is that DNA is not "naked" in all organisms that maintain a true nucleus (eukaryotes). Instead, the DNA exists as an intimate complex with specialized histone and nonhistone proteins, which together comprise chromatin. Although initially regarded as a passive packaging molecule to wrap and organize eukaryotic DNA, it is now clear and widely accepted that distinctive forms of chromatin arise through nucleosome arrays carrying covalent and noncovalent modifications. This process encompasses a plethora of post-translational histone modifications (see Sec. 5), energy-dependent chromatin-remodeling steps that mobilize or alter nucleosome structures (see Sec. 6), the dynamic shuffling of histone variants in and out of nucleosomes (see Sec. 7), and the targeting role of small ncRNAs (Sec. 11). DNA itself can also be modified covalently in many higher eukaryotes by methylation at the cytosine (C) residue, usually, but not always, of CpG dinucleotides (Sec. 10). Together, these mechanisms provide a set of interrelated pathways that create variation in the chromatin polymer (Fig. 3).

In isolation, the modifications and changes in chromatin are reversible and, therefore, unlikely to be propagated through the germline. Yet, such transitory histone modifications can impose pivotal changes to the chromatin template in response to intrinsic and external stimuli (Badeaux and Shi 2013; Suganuma and Workman 2013) and, in doing so, regulate the access of the transcriptional machinery needed to "read" the underlying DNA template (Sims et al. 2004; Petesch and Lis 2012; Smith and Shilatifard 2013). Some histone modifications (like lysine methylation), methylated DNA regions, ncRNAs, and altered nucleosome structures can, however, be stable through several cell divisions. This stability contributes to the maintenance of "epigenetic states," perhaps, as a means of achieving cellular memory, which is poorly understood. Despite a lack of mechanistic understanding, chromatin "signatures" can be viewed as a highly organized system of information storage that can segregate distinct regions of the genome to accommodate a response to environmental signals that dictate gene expression programs, which, in some cases, may be heritable.

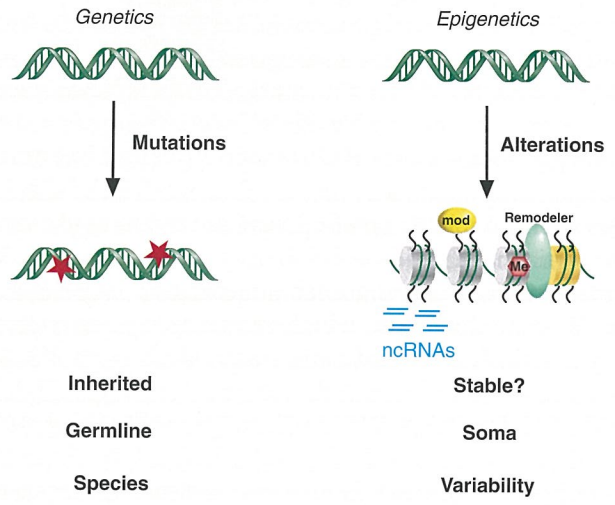

Figure 3. Genetics versus epigenetics. Genetics: Mutations (red stars) of the DNA template (green helix) are heritable somatically and through the germline. Epigenetics: Variations in chromatin structure modulate the use of the genome by (1) histone modifications (mod), (2) chromatin remodeling (remodeler), (3) histone variant composition (yellow nucleosome), (4) DNA methylation (Me), and (5) noncoding RNAs (ncRNAs). Marks on the chromatin template may be heritable through cell division and collectively contribute to determining cellular phenotype.

The significance of having a chromatin template that can potentiate the genetic information is that it provides multidimensional layers to the readout of DNA in keeping with the vast size and complexity of the eukaryotic genome, particularly, for multicellular organisms (see Sec. 13 for further details). In such organisms, a fertilized egg progresses through development, starting with a single genome that becomes epigenetically programmed to generate a remarkable multitude of distinct "epigenomes" in more than 200 different types of cells (Fig. 4).

The phenotypic alterations that occur from cell to cell during the course of development in a multicellular organism were originally described as an "epigenetic landscape" by the developmental biologist Conrad Waddington (Waddington 1957). This is essentially a contour map representing developmental potential, in which the combination of hills and valleys canalize the specification of cell type identities as development proceeds (an adaptation is illustrated in Fig. 1 of Ch. 2 [Takahashi 2014]). Yet, nearly all of the more than 200 cell types in humans share identical DNA sequences (with the exception of B and T cells that rearrange their antigen receptor loci), but differ remarkably in the profile of genes that they actually express. With this knowledge, "epigenetics" later came to be defined as "nuclear inheritance, which is not based on differences in DNA sequence" (Holliday 1994). In its more modern version, this sentence becomes molecularly (mechanistically) defined as the sum of the alterations to the chromatin template that collectively establish and propagate different patterns of gene expression (transcription) and silencing from the same genome.

4 THE CHROMATIN TEMPLATE

In its simplest form, the chromatin polymer is composed of repeating nucleosomal units, each consisting of an