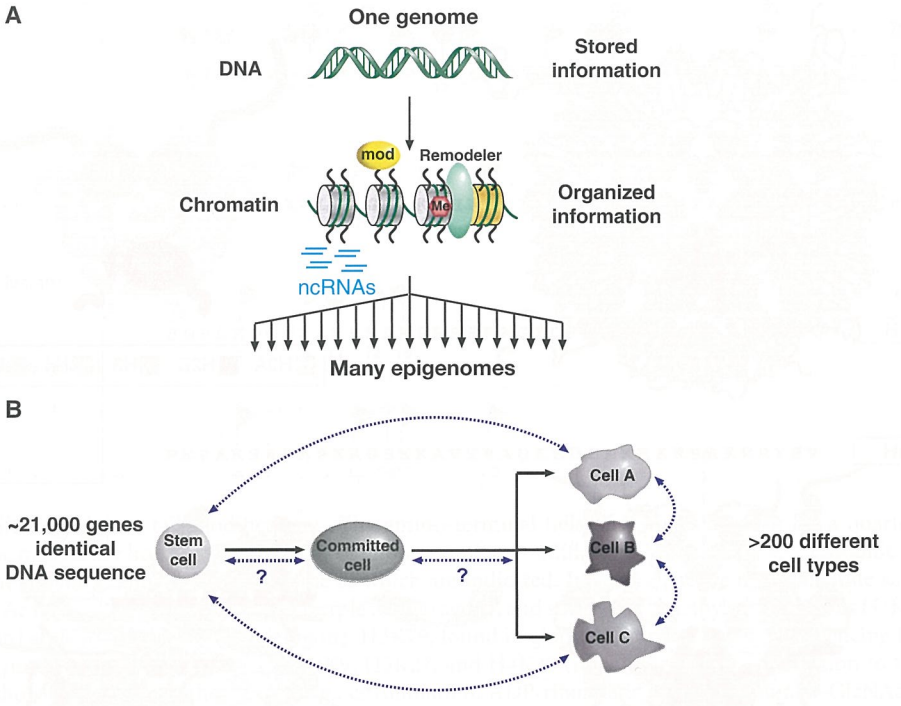

DNA versus chromatin. (*A*) The genome: Invariant DNA sequence (green double helix) of an individual. The epigenome: The overall n composition, which indexes the entire genome in any given cell. It varies according to cell type and response to internal and external eceives. (*B*) Epigenome diversification occurs during development in multicellular organisms as differentiation proceeds from a single the fertilized embryo) to more committed cells. Reversal of differentiation or change of cell type identities (blue dashed lines) requires gramming of the epigenome of the individual cells.

of histone proteins (i.e., two of each of the core H2A, H2B, H3, and H4) wrapped by 147 base p) of DNA (Kornberg 1977). Repeating arrays of ome particles had been seen early on in electron opic analyses of chromatin spreads, often des- the "bead-on-a-string" primary structure of chro- nd represents a form of euchromatin. But, outside epeating and particulate nature of chromatin, de- nucleosomal organization were unclear. Consid- nsights were gained into the nucleosome itself elegant biochemical studies (Kornberg 1974), con- ater by atomic resolution images of nucleosomes from X-ray crystallographic studies (Luger et al.

e landmark structures capture the disarming sim- ith which the nucleosomal unit is built; dimer sets ne partners (H2A with H2B) and tetramers (H3) engage each other in what is known as the "hand- otif," forming an octamer (Arents et al. 1991). elf organizes on the octamer surface leading to ll symmetric particle with a defined dyad axis. e crystal structures do not accurately portray the died histone tail domains that protrude from the histone DNA surface, giving rise to a flexible platform that carries many, but not all, of the posttranslational modifications (PTMs) that are described next.

5 HISTONE MODIFICATIONS: WRITERS AND ERASERS

The core histone proteins that make up the nucleosome are small and highly basic. They are composed of a globular domain and flexible (relatively unstructured) "histone tails," which protrude from the surface of the nucleosome (Fig. 5). Based on amino acid sequence, histone proteins are highly conserved from yeast to humans, supporting the general view that these proteins, even their unstructured tail domains, likely serve critical functions. The tails, particularly, of histones H3 and H4 hold important clues to nucleosomal and, hence, chromatin variability, as many of the residues are subject to extensive PTMs, as are some residues in the more structured globular core domains. The new studies of "human histone genetics," discussed above, wherein mutations in histones act as "onco-histones," underscore the importance of specific residues in histone H3 amino-terminal tails.