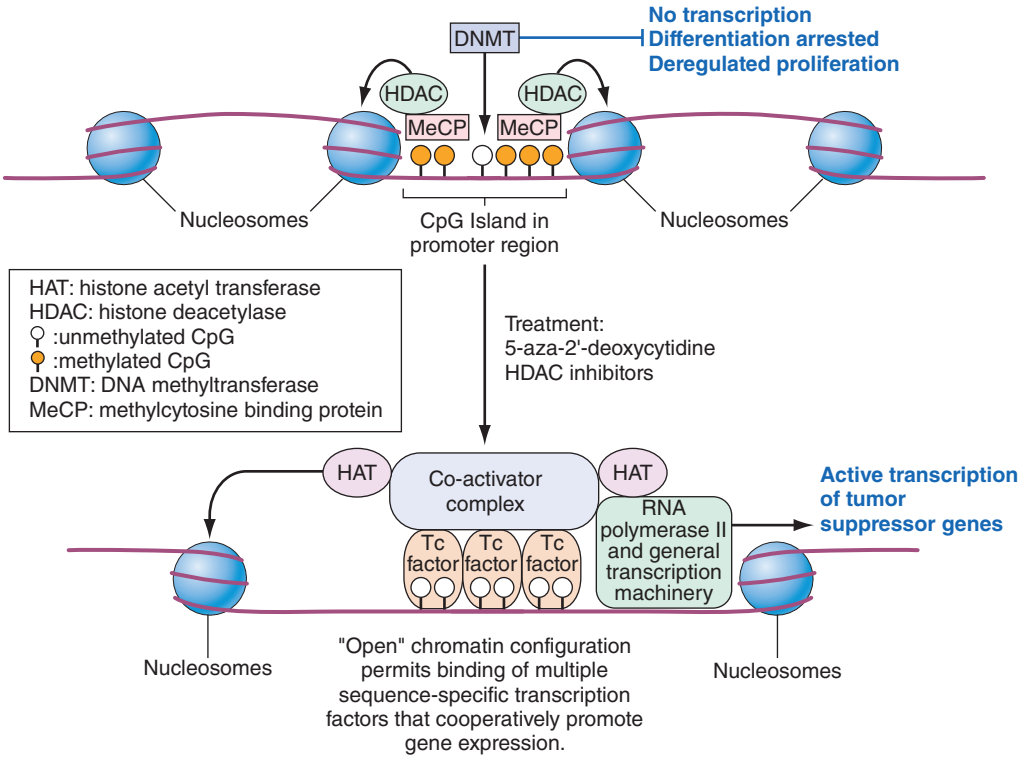

FIGURE 102e-4 Epigenetic regulation of gene expression in cancer cells. Tumor-suppressor genes are often epigenetically silenced in cancer cells. In the upper portion, a CpG island within the promoter and enhancer regions of the gene has been methylated, resulting in the recruitment of methyl-cytosine binding proteins (MeCP) and complexes with histone deacetylase (HDAC) activity. Chromatin is in a condensed, nonpermissive conformation that inhibits transcription. Clinical trials are under way using the combination of demethylating agents such as 5-aza-2′-deoxycytidine plus HDAC inhibitors, which together confer an open, permissive chromatin structure (*lower portion*). Transcription factors bind to specific DNA sequences in promoter regions and, through protein-protein interactions, recruit coactivator complexes containing histone acetyl transferase (HAT) activity. This enhances transcription initiation by RNA polymerase II and associated general transcription factors. The expression of the tumor-suppressor gene commences, with phenotypic changes that may include growth arrest, differentiation, or apoptosis.

being tested. HDAC inhibitors have demonstrated antitumor activity in clinical studies against cutaneous T cell lymphoma (e.g., vorinostat) and some solid tumors. HDAC inhibitors may target cancer cells via a number of mechanisms, including upregulation of death receptors (DR4/5, FAS, and their ligands) and $p21^{Cip1/Waf1}$, as well as inhibition of cell cycle checkpoints.

Efforts are also under way to reverse the hypermethylation of CpG islands that characterizes many malignancies. Drugs that induce DNA demethylation, such as 5-aza-2′-deoxycytidine, can lead to reexpression of silenced genes in cancer cells with restoration of function, and 5-aza-2′-deoxycytidine is approved for use in myelodysplastic syndrome (MDS). However, 5-aza-2′-deoxycytidine has limited aqueous solubility and is myelosuppressive. Other inhibitors of DNA methyltransferases are in development. In ongoing clinical trials, inhibitors of DNA methylation are being combined with HDAC inhibitors. The hope is that by reversing coexisting epigenetic changes, the deregulated patterns of gene transcription in cancer cells will be at least partially reversed.

Epigenetic gene regulation can also occur via microRNAs or long non-coding RNAs (lncRNAs). MicroRNAs are short (average 22 nucleotides in length) RNA molecules that silence gene expression after transcription by binding and inhibiting the translation or promoting the degradation of mRNA transcripts. It is estimated that more than 1000 microRNAs are encoded in the human genome. Each tissue has a distinctive repertoire of microRNA expression, and this pattern is altered in specific ways in cancers. However, specific correlations between microRNA expression and tumor biology and clinical behavior are just now emerging. Therapies targeting microRNAs are not currently at hand but represent a novel area of treatment development. lncRNAs are longer than 200 nucleotides and compose the largest group of noncoding RNAs. Some of them have been shown to play important roles in gene regulation. The potential for altering these RNAs for therapeutic benefit is an area of active investigation, although much more needs to be learned before this will be feasible.

APOPTOSIS AND OTHER MECHANISMS OF CELL DEATH

Tissue homeostasis requires a balance between the death of aged, terminally differentiated cells or severely damaged cells and their renewal by proliferation of committed progenitors. Genetic damage to growth-regulating genes of stem cells could lead to catastrophic results for the host as a whole. Thus, genetic events causing activation of oncogenes or loss of tumor suppressors, which would be predicted to lead to unregulated cell proliferation unless corrected, usually activate signal transduction pathways that block aberrant cell proliferation. These pathways can lead to a form of programmed cell death (*apoptosis*) or irreversible growth arrest (*senescence*). Much as a panoply of intra- and extracellular signals impinge upon the core cell cycle machinery to regulate cell division, so too are these signals transmitted to a core enzymatic machinery that regulates cell death and survival.

Apoptosis is induced by two main pathways (Fig. 102e-5). The extrinsic pathway of apoptosis is activated by cross-linking members of the tumor necrosis factor (TNF) receptor superfamily, such as CD95 (Fas) and death receptors DR4 and DR5, by their ligands, Fas ligand or TRAIL (TNF-related apoptosis-inducing ligand), respectively. This induces the association of FADD (Fas-associated death domain) and procaspase-8 to death domain motifs of the receptors. Caspase-8 is activated and then cleaves and activates effector caspases-3 and -7, which then target cellular constituents (including caspase-activated DNAse, cytoskeletal proteins, and a number of regulatory proteins), inducing the morphologic appearance characteristic of apoptosis, which pathologists term "karyorrhexis." The intrinsic pathway of apoptosis is initiated by the release of cytochrome *c* and SMAC (second