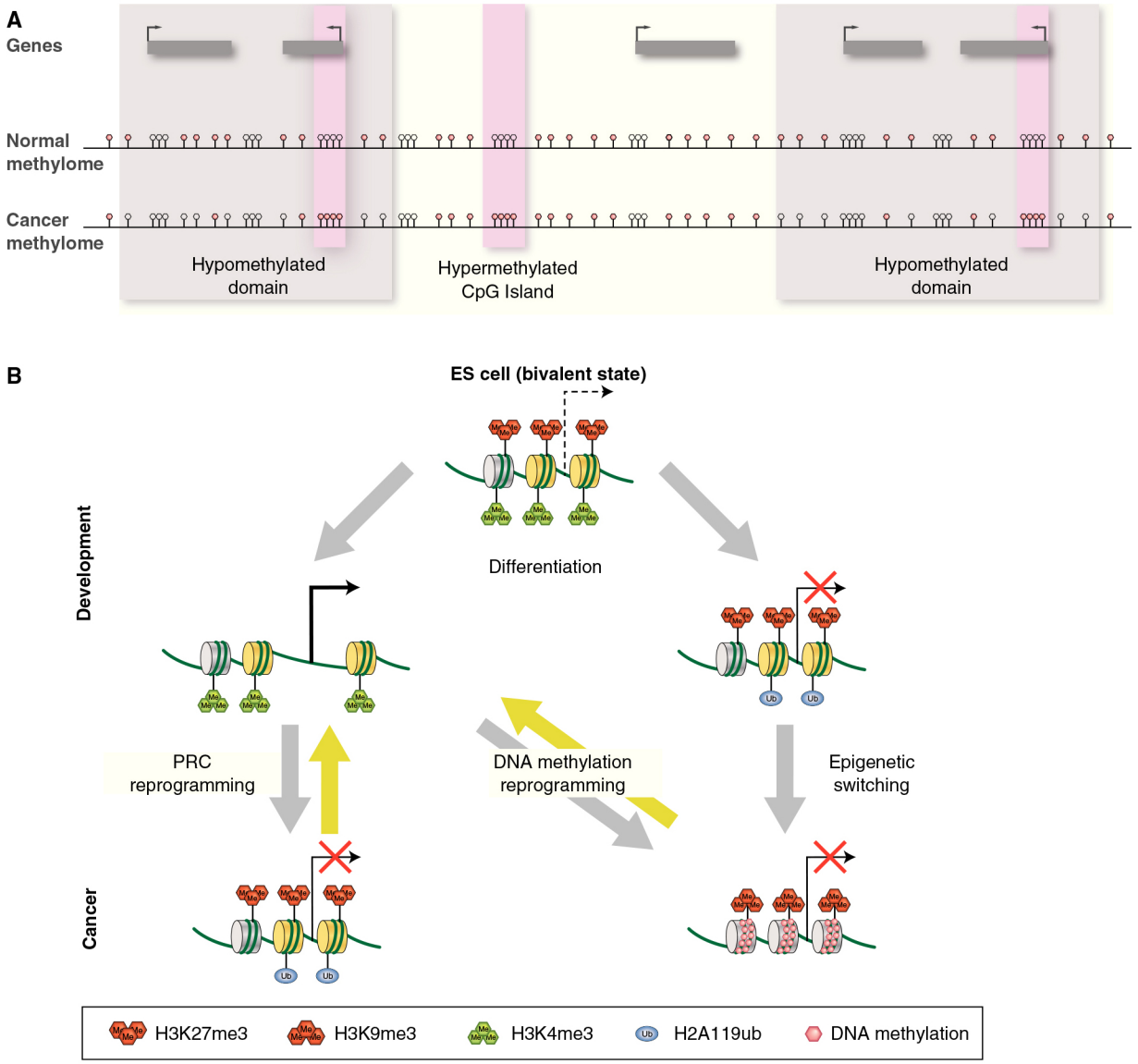

Figure 7. Reprogramming of DNA methylation patterns and abnormal modes of gene silencing in cancer. (*A*) Common DNA methylome changes observable in cancer versus a normal somatic cell are illustrated. This is shown in the context of large hypomethylated blocks (gray shading) of the genome seen in cancer interspersed with focal hypermethylation of promoter region CpG-island-containing genes (pink shading). In normal cells, background DNA methylation is high (pink shaded hexagons) with the exception of CpG islands (densely packed white shaded hexagons). In the cancer methylome, overall genome DNA methylation declines, particularly in the hypomethylated blocks, whereas CpG island promoter genes frequently become methylated (pink shading), most of which are located in the hypomethylated blocks. (*B*) The currently suggested routes to abnormally silenced CpG-island-containing genes in cancer are shown. Genes that are active in cells throughout development and adult cell renewal initially have active promoter chromatin, which is characterized by the presence of the bivalent histone modification pattern consisting of H3K4me, the repressive H3K27me3 mark, and a lack of DNA methylation. Genes that become transcriptionally active lose much of their Polycomb-mediated repressive H3K27 methylation, whereas those that become silenced (indicated by a red X) can do so by the loss of H3K4 methylation and acquisition of, or increases in, Polycomb-mediated repressive chromatin (PRC) mark and H2A119 ubiquitination. During tumor progression, active genes may become silenced through either the aberrant PRC-mediated reprogramming (*bottom left*) or DNA methylation and H3K9me marks (*bottom right*). Some normally silent genes may change the way in which they are transcriptionally repressed from H3K27-methylation-type repression to H3K9-methylation-based silencing and/or DNA hypermethylation (epigenetic switching). The reverse yellow arrows indicate the potential for epigenetic abnormalities in cancer to be corrected by epigenetic therapies. Representative of such therapies are DNMT inhibitors, HDAC inhibitors, KMT inhibitors, and others, as discussed in this and other chapters. These inhibitors can all potentially promote gene activation by producing losses of DNA methylation, or deacetylating lysines, or alleviating silencing mediated by histone methylation PTMs, such as H3K27 methylation. (*A*, Adapted from Reddington et al. 2014; *B*, adapted from Sharma et al. 2010.)