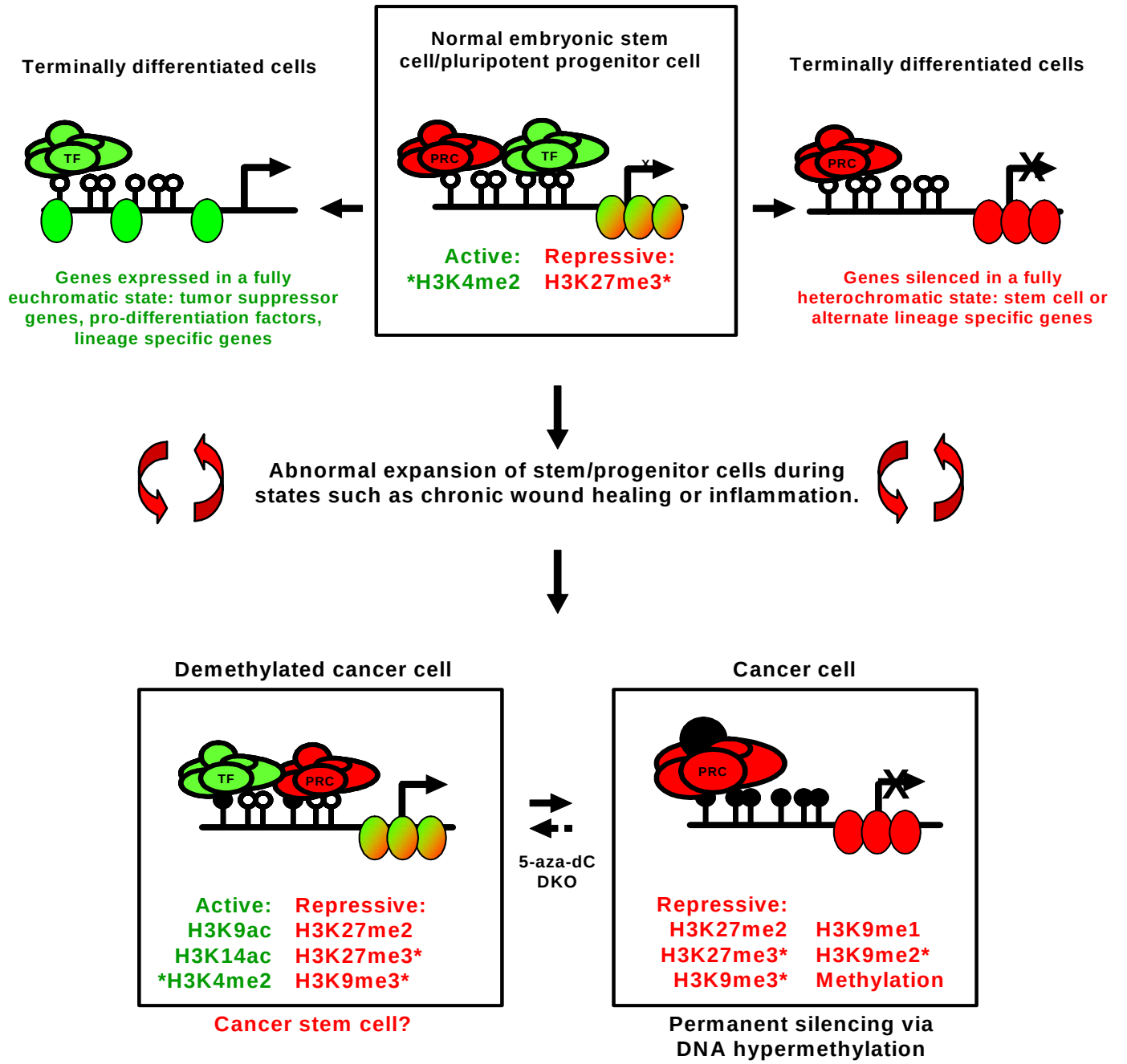
Supplementary Figure 1.



Model for how abnormal DNA methylation may be recruited to most tumor suppressor genes in adult cancer cells, reflecting a stem/progenitor cell of origin. The promoter chromatin state for many genes that are frequently DNA hypermethylated in cancer is virtually identical between embryonic and adult stem and precursor cells and adult cancer cells. This "bivalent" chromatin state is characterized by simultaneous presence of both key active and repressive histone modifications and gene silencing polycomb group (PcG) proteins, and is also similar to that of CpG island promoters of multiple, developmentally related, genes which have low expression in ES cells 17,20. During states of abnormal cell renewal, such as chronic injury repair during inflammation, there is expansion of adult stem or precursor cells with the above bivalent chromatin states at the genes we have studied. The presence of PcG proteins and H3K27me3, plus addition of H3K9me2, may be responsible for recruitment of abnormal DNA methylation to CpG islands at the gene promoters and this leads to cells with heritable, deep silencing of these genes. The loss of function of these genes, in turn, locks stem/precursor cells into abnormal clonal expansion which begins a process of neoplastic initiation and progression. *indicates chromatin marks assayed in this study.