Epigenetics in Cancer

Epigenetics can be defined as acquired changes in chromatin structure that arise independently of a change in the underlying DNA nucleotide sequence. Epigenetic modifications such as acetylation, methylation and ubiquitination can alter the accessibility of DNA to transcription machinery and therefore influence gene expression. The dysregulation of these epigenetic modifications has been shown to result in oncogenesis and cancer progression. The cell cycle, as well as proliferation and metastasis can be regulated by histone modification, DNA methylation and chromatin remodeling. Unlike genetic mutations, epigenetic alterations are reversible and thus make promising therapeutic targets.

Epigenetic Mechanism

The fundamental unit of chromatin is the nucleosome, which consists of an octamer of the histone proteins H2A, H2B, H3 and H4 (two of each) tightly bound by DNA. Alterations in chromatin structure by post-translational modifications can regulate gene expression through the formation of heterogeneous chromatin or euchromatin, which usually activate or repress gene transcription, respectively. Post-translational modifications include DNA methylation and the covalent modifications (Me and acetylation) of histone tails. DNA methylation represses transcription by blocking the binding of transcription complexes to the gene promoter. The acetylation of histone tails usually increases access to DNA from the nucleosomes, increasing the accessibility of gene promoters to transcription complexes, therefore promoting transcription. Histone tail methylation can repress or promote gene expression, depending on the site and context of the modification, as well as the presence of other histone modifications in the vicinity. The pattern of these post-translational modifications on a nucleosome determines the transcriptional profile of nearby genes. For example, histone chaperones direct CHD1, part of the Polycomb Repressive Complex 2 (PRC2), to repress the target genes through the tri-methylation of lysine 27 on histone H3 (H3K27me3). The functions of histone acetylation are less well understood. However, increasing evidence points to an important role for this histone modification in the DNA damage response.

Types of Epigenetic Modifications

Proteins that carry out these epigenetic modifications can be thought of as being either “writers,” “readers” or “erasers.”

- **Writers** - catalyze the addition of epigenetic marks onto either histone tails or the DNA itself
- **Readers** - recognize and are recruited to specific epigenetic marks. “Writer” and “eraser” enzymes may also contain such reader domains, leading to the concept of “read-write” or “read-erase” mechanisms.
- **Erasers** - remove epigenetic marks to alter gene expression

BRD Inhibition Suppresses Tumor Growth and Metastasis

Bromodomains (BRDs) are epigenetic “readers” that selectively recognize acetylated lysine residues on histone protein tails. Of particular interest is the BET bromodomain (extra-terminal) bromodomain, which is the bromodomain commonly targeted by BET inhibitors. BET bromodomains are highly conserved across species and are often referred to as the “hallmark” of the BET family. However, this approach can result in drug resistance and toxicity issues. Therefore, more selective BET inhibition is necessary to achieve effective therapeutic responses.

In vivo studies have shown that inhibition of BRD4 impairs tumor growth and metastasis. In a mouse model of JQ1-resistant triple-negative breast cancer, while dBET1 induces BRD4 protein degradation, in another study, suppression of BRD4 protein expression in an ovarian cancer cell line was accompanied by decreased cell viability in a xenograft model of ovarian cancer and thus resulted in tumor growth inhibition. The cell cycle, as well as proliferation and metastasis can be regulated by histone modification, DNA methylation and chromatin remodeling. Unlike genetic mutations, epigenetic alterations are reversible and thus make promising therapeutic targets.

### References

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