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 and metastasis can be regulated by histone modification, DNA methylation and chromatin remodeling. Unlike genetic mutations, epigenetic alterations are considered to be reversible and thus make a promising therapeutic target.

Types of Epigenetic Modifiers

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

- **Epigenetic writers** catalyze the addition of epigenetic marks onto either histone tails or the DNA itself.
- **Epigenetic reader domains** are effector proteins that recognize and are recruited to specific epigenetic marks. “Writer” and “eraser” enzymes may also contain such reader domains, leading to the coordination of “read-write” or “read-erase” mechanisms.
- **Epigenetic 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 and extra-terminal) bromodomain family, which comprises the ubiquitously expressed proteins BRD2, BRD3, BRD4, and the testis-specific protein, BRDT. BET proteins are epigenome readers that play a key role at the interface between chromatin remodeling and transcriptional regulation, and are integral in the regulation of transcriptional elongation and the cell cycle. BRD4 influences mitotic progression and is critical in the regulation of transcriptional elongation and the cell cycle. BRD4 regulates mitotic progression and is a critical mediator of transcriptional elongation because it binds to transcriptional sites of genes expressed during the M/G1 cell cycle transition. BRD4 increases expression of genes that promote growth by recruiting p-TEFb to mitotic chromosomes. Furthermore, it has been observed that BRD4 is significantly upregulated in both primary and metastatic melanomas. In vivo studies have shown that inhibition of BRD4 impairs tumor growth and metastasis.

Key BRD4 inhibitors include the potent, high affinity and selective, arylcycloalkene bromodomains inhibitor (I-BET), which induces squamous cell differentiation and arrests tumor growth in BRD4-dependent carcinomas, including tumor growth in midline carcinoma cell xenograft models. I-BET151 potently blocks recruitment of BRD4 to chromatin, inducing apoptosis and cell cycle arrest in MLLFusion leukemia cell lines. This compound has also been shown to improve survival in rodent models of MLLFusion leukemia.

E3 ligase

- **E3 ligase**
  - Inhibitors: SCLP2-41, SKP1C1, SMER3

DUB Inhibitors

- **DUB Inhibitors**: P 22077, PD03591, Spautin1

DNMT Inhibitors

- **DNMT Inhibitors**: 6-Thioguanine, Zebularine, Decitabine

KDM/PRMT Inhibitors

- **KDM/PRMT Inhibitors**: UNC0642, UNC1999, Rp-FPI2, SGC0946, C21, TC-E5003

HDAC Inhibitors

- **HDAC Inhibitors**: Trichostatin A, FK228, SAHA, Valproic acid

BRD Inhibitors

- **BRD Inhibitors**: CPI203, I-BET151, (+)-JQ1, MS436

Abbreviations:

- **BRD**: Bromodomains
- **DNMT**: DNA methyltransferases
- **KDM**: Histone demethylases
- **PRMT**: Protein Arginine Methyltransferases
- **HAT**: Histone acetyltransferases
- **HDAC**: Histone deacetylases
- **KMT**: lysine methyltransferases
- **DUB**: deubiquitinating enzymes
- **DNMT**: DNA methyltransferases
- **HDAC**: Histone deacetylases
- **KMT**: lysine methyltransferases
- **PRMT**: Protein Arginine Methyltransferases

Products available from Tocris

14-3-3 Proteins

- Difopein

Aurora Kinases

- Anacardic acid, CCT 137690, Hesperadin, PF... Product Guide

To request a copy of the Tocris Cancer Product Guide, or to view the PDF, please visit www.tocris.com

Epigenetics in Cancer

Adapted from Edition 3 of the Tocris Cancer Product Guide

To request a copy of the Tocris Cancer Product Guide, or to view the PDF, please visit www.tocris.com

References:

- Suva et al. (2013) Epigenetic reprogramming in cancer.
- Muller et al. (2011) Bromodomains as drug discovery.
- Science 359.
- 1567.
- 1511.
- 1528.
- 1536.
- 1569.
- 1581.
- 1599.
- 1607.
- 1615.
- 1623.
- 1631.
- 1639.
- 1647.
- 1655.
- 1663.
- 1671.