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EPIGENETIC TARGETS ARE A RICH VEIN OF ORIGINAL DRUGS

As HISTONE METHYLTRANSFERASE inhibitors advance through clinical trials, researchers accelerate the search for other epigenetic drug targets.

In the crowded world of drug discovery, opportunities for first-in-class medicines are rare. Epigenetics, which determines how genes are expressed, may prove an exception. There is a growing awareness that epigenetic dysregulation plays a significant role in many types of cancer, and that is fuelling an increasing number of studies into drugs that target epigenetic regulators.

Such regulatory proteins fall into three main categories: writers, readers and erasers. Writers 'mark' histones and DNAs by adding chemical groups, indicating either transcription, replication or repair. Modifications include acetylation, phosphorylation and methylation. Readers recognize and act upon the modifications, whereas erasers remove them (see 'The epigenetic landscape').

Several drugs that inhibit epigenetic writers and erasers have been approved by the US Food and Drug Administration (FDA) for the treatment of cancer. These include DNA methyltransferase and histone deacetylase (HDAC) inhibitors. Further candidates, including inhibitors of acetyl-lysine readers (bromodomain-containing proteins), are undergoing clinical evaluation for efficacy in different cancer settings.

Among the various drug targets, histone methyltransferases (HMTs) have emerged as particularly attractive. Not only have HMT mutations been associated with disease, but also structural and mechanistic data indicate they could be modulated by small molecules.

Several HMT inhibitors are in clinical trials. Should any receive regulatory approval, they would be first-in-class drugs and could offer new hope to patients for whom standard treatments have failed.

HMT inhibitors in clinical trials

Of the many HMT targets under investigation, one of particular note is the enhancer of zeste homologue 2 (EZH2). Mutations and overexpression of EZH2 have been associated with numerous human cancers, including prostate, breast, skin, liver, lung and gastric cancers, as well as lymphomas and myelomas.

Both of the orally available candidate drugs, tazemetostat and CPI-1205, selectively inhibit the activity of wild-type and mutated forms of EZH2. They are currently in clinical trials for various types of cancer. Interim data from the phase II trial for tazemetostat showed evidence of efficacy in patients with relapsed or refractory follicular lymphoma or diffuse large B-cell lymphoma.

Other promising HMT-targeting drugs undergoing first-in-human studies are pinometostat, an inhibitor of disruptor of telomeric silencing 1-like (DOT1L) HMT, and GSK3326595, which inhibits the arginine methyltransferase 5 (PRMT5) protein.

Pinometostat has shown an acceptable safety profile in phase I clinical trials for the treatment of acute leukemia; its effects will continue to be investigated in combination with other agents. GSK3326595 is currently undergoing a phase I clinical trial in patients with solid tumors and non-Hodgkin's lymphoma; preliminary results are expected in 2019.

Advances in targeting epigenetic readers

Epigenetic readers are also emerging as a promising new drug target class. These bromodomain-containing proteins recognize acetylation marks on histones, and regulate chromatin structure and gene expression by recruiting additional regulatory proteins, such as transcription factors.

Members of the bromodomain and extraterminal domain (BET) family of epigenetic regulators have been shown to directly regulate the expression of cancer-related genes. Potent and selective inhibitors that target BET proteins can block their interaction with acetylated histone residues and decrease the expression of genes associated with cancer and inflammatory responses.

BET inhibitors in phase I trials include CPI-0610 for hematological malignancies, and birabresib (OTX-015/MK-8628) for diffuse large B-cell lymphoma. Both compounds show potent anticancer activity and good tolerability so far.

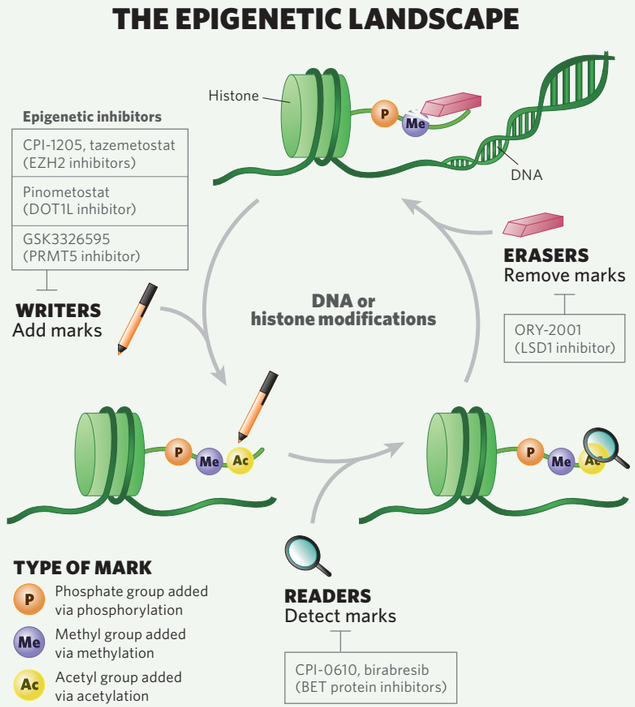
Beyond cancer indications

Although cancer has been the main focus of epigenetic research, there is growing interest in exploring epigenetic-based therapies for other conditions, such as inflammatory diseases, chronic pain states, obesity, diabetes, neurodegeneration and viral infection.

Disease modifying drugs are urgently needed for Alzheimer's disease. Many researchers and investors are excited by the announcement in April 2018 that ORY-2001 — an orally available selective inhibitor of lysine-specific demethylase (LSD1) and monoamine oxidase B — will be tested in a phase IIa clinical trial in patients with mild-to-moderate Alzheimer's disease. Previous work has shown that the compound can reduce cognitive impairment, memory loss and neuroinflammation.

Viruses depend on a host's epigenetic machinery to both replicate and cause latent infection. Some epigenetic drugs designed to treat cancer have the potential to be used as broad-spectrum antivirals. HMT EZH2/1 inhibitors can prevent viral gene expression and reduce herpes simplex virus infection in mice.

In the case of latent infections, re-activation of viral genes is required to completely eradicate the virus. Targeting epigenetic regulators has again proved a useful strategy for this with several BET bromodomain inhibitors showing promise in the re-activation of latent HIV in patient derived CD4+ T cells.



Epigenetic regulators control protein function and stability as well as gene transcription, DNA replication and DNA repair. Importantly, they induce potentially heritable changes of gene function without modifying the underlying DNA sequence.

Epigenetic writers mark the DNA or histones. This family includes histone acetyltransferases (HATs), histone methyltransferases (HMTs), protein arginine methyltransferases (PRMTs) and kinases.

Epigenetic readers, such as proteins containing bromodomains, chromodomains and Tudor domains, bind to these epigenetic marks and recruit other chromatin regulators.

Epigenetic erasers such as histone deacetylases (HDACs), lysine demethylases (KDMs) and phosphatases, catalyse the removal of epigenetic marks.

Mutations that affect the functions of epigenetic regulators are associated with cancer and various immunological and neurodegenerative conditions.

Understanding these dysfunctions could explain why one person with a genetic disposition to a certain type of cancer becomes ill whereas another person with the same gene variant stays healthy. Thus, the study of epigenetic alterations not only offers novel therapeutic approaches for many clinical indications but will also contribute to realizing the promise of personalized medicine.

Several drugs targeting epigenetic writers and erasers are already in the clinic and many more, including reader inhibitors, are progressing through clinical trials.

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Encouraging discovery

As researchers deepen their focus on epigenetic drug targets, the need for reliable, structure-guided discovery methods and high-throughput screening of chemical libraries is paramount.

Reaction Biology Corporation (RBC), in Malvern, Pennsylvania, is the provider of choice for pharmaceutical, biotech, government and academic laboratories worldwide.

In the realm of HMT profiling, "RBC has been developing and providing HMT assay services since 2008 with the support of the NIH's Small Business Innovation Research grants", says Haiching Ma, RBC's Chief Science Officer. "RBC's scientific team has extensive experience in this area and one of the largest HMT service portfolios", he adds.

RBC offers more than 30 highly active methyltransferase enzymes and more than 20 specific substrates, along with a number of different assay formats and services including: high-throughput screening, panel profiling and mechanism of action studies with surface plasmon resonance, isothermal titration calorimetry, microscale thermophoresis and thermal shift assays plus follow-up cell-based activity confirmations.

RBC's HotSpot℠ HMT assays offer high-quality screening data and require no substrate modification, coupling enzymes or detection antibodies. Whether used with nucleosome, histone or peptide substrates, the radiolabelled HotSpot℠ format eliminates the possibility of compound assay interference and represents the gold standard of HMT assay technologies.

To address the growing demand for BET inhibitor profiling, RBC has developed a variety of bromodomain assays, including AlphaScreen, HTRF, Thermal Shift and isothermal titration calorimetry assays. These can be used for screening, lead optimization or selectivity profiling to identify bromodomain inhibitors.

RBC's latest bromodomain product is the BromoMELT™ assay kit, which can test the selectivity of any compound against 53 of the 61 members of the human bromodomain family. BromoMELT™ measures the thermal stability of a target protein and the increase in protein melting temperature upon the binding of a ligand to the protein. This is not only useful for identifying ligands but also for optimizing buffer conditions and other factors that affect protein stability.

As the therapeutic potential of epigenetic therapies unfolds, and high-quality assays are introduced, the prospect of game-changing drugs with fundamentally new mechanisms of action draws closer.

Further information about RBC: www.reactionbiology.com

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