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The rise of epigenetic targets for the development of novel antivirals

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"…the complex regulatory machineries that assemble, modify, recognize and remodel nucleosomes … represent a large collection of targets for the development of an array of potentially broad-spectrum antivirals."

Epigenetics

Access to the eukaryotic genome for purposes of gene transcription, DNA replication and DNA repair is restricted or facilitated by the 'epigenetic' supraregulatory overlay of both DNA modifications and the modulation of nucleosomes and higher-order chromatin structure. Complex regulatory machinery consisting of multiple families of protein complexes are dedicated to DNA methylation–demethylation, nucleosome assembly–disassembly, histone modification, modification recognition, nucleosome remodeling and recruitment of components that promote or inhibit access of transcriptional or replicative factors to the genome.

Epigenetic approaches in cancer therapies

Significantly, many cancers reflect altered epigenetic control of the expression of key cellular regulators. The rapid delineation of the components that modulate chromatin and the significance of the impact of chromatin in gene transcription, cell differentiation and organismal development have incited the search or design of compounds that target specific chromatin regulators. The ability to modulate the activity of chromatin enzymology and chromatin recognition to reset the epigenetic base is rapidly providing novel approaches to the treatment of various types of cancers [1–4].

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Epigenetic inhibition of herpesvirus lytic infection

Like their host cells, many invading viral pathogens are also modulated by chromatin. The genomes of large dsDNA viruses such as the family of herpesviruses are packaged into viral capsids in the absence of nucleosomes. Upon infection, these genomes are rapidly assimilated into nucleosomal chromatin structures, and thus become subject to the host cell's chromatin regulatory machinery [5–12]. While mechanistically unclear, cell-mediated assembly of nucleosomes on the viral genome is initially repressive to the expression of viral genes as the nucleosomes bear high levels of repressive histone marks [7–9,11]. Viruses such as herpes simplex virus (HSV) circumvent this repression by recruiting cellular chromatin modification enzymes including the lysine specific demethylase-1 (LSD1) [8,9] and the family of JMJD2 demethylases to the viral genome, promoting the removal of these repressive marks and allowing for the installation of positive marks that facilitate viral gene expression. Failure to circumvent this repression results in suppression of the first class of viral genes and abrogation of infection. Therefore, small molecule inhibition of these enzymes has the potential to block productive lytic infection at a very early stage of infection. The principle has been clearly demonstrated *in vitro* as inhibition of the enzymatic activity of LSD1 via monoamine oxidase inhibitors (i.e., tranylcypromine) blocks viral gene expression and abrogates infection [9]. In addition, initial animal model studies also demonstrate suppression of primary HSV infection *in vivo*.

Epigenetic targeting of herpesvirus reactivation from latency

In addition to the lytic replication cycle, primary infection with HSV or other members of the herpesvirus family results in establishment of lifelong latent-persistent infections where reactivation from the latent state causes recurrent disease. It has been well established that chromatin modulation plays a significant regulatory role in determining the latency-reactivation cycles of several herpesviruses [5,7,11–13]. In these studies, the transition from the latent state to the lytic replication cycle is paralleled by removal of repressive histone modifications that suppress viral lytic gene expression.

For HSV, latency is established in sensory neurons proximal to the site of initial infection. Reactivation can result in mild oral or genital lesions but may also produce more significant illness such as HSV keratitis, a leading cause of blindness; blindness and persistent neurological issues resulting from initial congenital infections; and increased HIV transmission in coinfected individuals. Other members of the herpesvirus family with similar regulatory paradigms such as human cytomegalovirus represent clinical challenges for immunocompromised individuals; solid organ transplant where a large percentage of transplanted organs are either infected or the transplant results in reactivation of latent human cytomegalovirus in the recipients; and congenital infections where human cytomegalovirus is a significant causative agent of birth defects.

Infections and cycles of reactivation are typically controlled by 'late-stage' DNA replication inhibitors (i.e., acycloguanosine and derivatives). However, treatment can result in the emergence of resistant strains. In addition, these compounds do not prevent the expression of many early viral lytic genes, ultimate destruction of the infected cells, and the associated

immune inflammatory damage. Most significantly, these pharmaceuticals do not eliminate subclinical viral shedding, a significant mode of transmission.

Strikingly, in a manner analogous to the lytic replication cycle, small molecule inhibitors of LSD1 or JMJD2 proteins block HSV reactivation from latency in a mouse sensory ganglia explant model system [9]. Most significantly, the ability to suppress the initial events in viral reactivation is anticipated to suppress spontaneous reactivation, subclinical viral shedding and associated inflammatory damage. In addition, as these compounds target host- rather than viral-encoded factors, the emergence of resistant strains would not be expected. Thus, the complex regulatory machineries that assemble, modify, recognize and remodel nucleosomes and chromatin-associated proteins represent a large collection of targets for the development of an array of potentially broad-spectrum antivirals.

Concepts in ‘chromatin-based treatments’ of nonherpesvirus pathogens

The persistence of human papillomaviruses may also be receptive to chromatin-based therapeutics. These viruses are maintained and transmitted to daughter cells during cell replication via tethering to chromatin recognition proteins including the histone acetyl-recognition protein Brd4 [14]. While not yet demonstrated, the potential to disrupt this transmission via a new class of bromodomain protein inhibitors [15] is intriguing.

In addition to these classes of DNA viruses, the persistence of viruses such as HIV also depends on chromatin modulation. For lytic replication, the demethylase LSD1 is required for efficient viral transcription and activation via modulation of the methylation state of the HIV activator TAT [16]. Phenotypically similar to HSV, inhibition of LSD1 results in silencing of the virus.

> “…many invading viral pathogens are also modulated by chromatin.”

In another HIV regulatory paradigm, chromatin components that maintain the proviral latent state also represent important therapeutic targets. While highly active antiretroviral therapy therapy has vastly improved the clinical outcomes of infection, the latent pool of provirus remains inaccessible to treatment. Elucidation of the roles of specific histone deacetylase complexes in maintaining the proviral silent-latent state has now given rise to the concept of forced reactivation clearance [17]. Here, inhibition of the repressive activities of histone deacetylase complexes can result in reactivation of the latent provirus, thus making the infected cells targets for clearance.

Current standing & moving forward

Advancements in understanding dynamic interactions of viruses with cellular chromatin and chromatin modulation components continue to elucidate novel targets. The development of specific inhibitors has tremendous potential for new classes of antivirals and new promise of novel approaches to reducing or eliminating latent viral pools. At present, model systems have clearly demonstrated the potential of these approaches. However, concerted efforts to recognize and drive these approaches to clinical therapies are needed. As there have been significant advances in the development of inhibitors or other chromatin modulation

compounds for oncology, the parallels of chromatin modulation in viral diseases should be clearly recognized and considered.

Modulation of viral infection by chromatin is moving into the coordinated scientific assessment of the epigenomes of various viral families. It is likely that, as the databases of the state of viral chromatin grows, additional regulatory circuits will become more fully understood with respect to variances between viral states, cell-type dependence and specific modulation components. Intense efforts are being made to develop a range of compounds targeting chromatin regulatory and recognition components for oncology. Coupled with the appreciation that viral pathogens can also be modulated should bring additional focus on the broader nature of chromatin-based therapies.

Other exciting avenues in chromatin control of infection that are likely to be significant are based upon chromatin-mediated regulation of the cellular antiviral response [18,19] and control of inflammation [20]. Specifically, as chromatin modulates the induced transcription of interferon-dependent genes and pro-inflammatory genes in response to viral infection, these processes will be important chromatin therapeutic targets to both enhance cellular responses and limit inflammatory damage.

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Biography

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