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Editorial
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Histone Deacetylases and Radiation Therapy: Current Status and Gazing Towards the Future

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Editorial

Radiotherapy remains one of the most prevalent forms of cancer treatment, with approximately 50% of all cancer patients receiving some form of radiation treatment throughout the course of their illness [1]. In short, radiotherapy aims to deprive cancerous cells of their multiplicative ability through the initiation of DNA double-stranded breaks (DSB). Yet, cells have mechanisms to repair such DSB — non-homologous end-joining (NHEJ) [2] and homologous recombination (HR) [3] — allowing the continued proliferation of cancer even after intense radio treatment. Nearly 60% of all patients remain uncured after radio treatment [1]. Notably, histone deacetylase inhibitors (HDACi), when used in combination with traditional radiotherapy, have shown promising anticancer effects. Although the underlying mechanism is not fully uncovered, studies have shown that HDACi prevent DSB repair which in turn mediates, at least in some significant part, the radio sensitization of cancerous cell lines.

HDACs and HDACi

The identification of cancer as a result of both epigenetic changes, either genome-wide or more restricted, and altered expression of regulatory proteins provides strong basis for the use of epigenetic-based therapies [4]. Focusing on aberrant histone modifications as critical epigenetic events, histone acetylation is fine-tuned through the opposing actions of histone acetyl transferases which activate transcription and histone deacetylases (HDAC) which repress transcription. As enzymatic activity inhibition is a pharmacologically viable approach, this strategy has been therapeutically explored to specifically target significant HDAC. Given their role in creating non-permissive chromatin conformations that prevent the transcription of genes involved in tumorigenesis, HDAC inhibition could result in chromatin remodeling and transcriptional activation of tumor suppressors as an anti-cancer strategy [5,6].

Interestingly, several genes have been reported to be down regulated upon HDAC inhibition, contradictory to the often positive effect of acetylation on gene transcription. This effect seems to be critical for HDACi ability to mediate and impair cellular capacity to repair damaged DNA. It has been shown that HDACi can prevent NHEJ by down regulating the core NHEJ proteins that make up the Ku heterodimer recruitment during the reparative process [7-9]. Moreover, HDACi have also been shown to down regulate RAD51 protein expression, preventing the formation of the RAD51 nucleoprotein filament needed to initiate sister chromatid invasion during HR [7,8,10]. By impeding the two major mechanisms involved in DNADSB repair, HDACi cause cells to arrest in the cell cycle, consequently resulting in apoptosis and preventing further propagation.

Combination of HDACi and Radiotherapy Rationale

Because of its ability to impede DNA repair, HDACi therapeutics appear to be most effective when used in combination with traditional radiotherapies. Since 1896 when Chicago-based physician Dr. Emil Grubbe introduced the concept of radio oncology after treating a recurrent breast cancer patient with radiotherapy, treatments using ionizing radiation have been extensively used due to their effectiveness in inducing DSB [11]. Therefore, use of HDACi in conjunction with this existing form of treatment appears to be the most effective way to maximize radio sensitizing effects. This is evidenced by several clinical studies confirming that HDACi reduce cellular capacity to repair DNA in prostate, glioma, melanoma, squamous cell, osteosarcoma and glioblastoma cancers [10,12-14].

The therapeutic potential of HDACi is further established by studies showing that several prominent inhibitors do not radio sensitize normal, noncancerous cells [8]. NaB, a popular HDACi,

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did not radio sensitize normal human lung fibroblasts [8]. Vorinostat, another common HDACi, did not affect the radio sensitivity of both osteoblast and fibroblast cell lines [8,15]. The apparent specificity of HDACi towards cancerous cells seems to suggest that effective doses of HDACi for treating cancer are below the toxicity threshold of normal cell lines. Relevantly, further research pinpointing the precise pathways and targets of existing HDACi will significantly contribute to more effective radio sensitization of cancer cells, combined with further cytoprotection of normal cells.

Promise/Existing Studies

Building upon the promising pre-clinical results, a few HDACi have been approved by the FDA either as monotherapy or combination therapy tools, including vorinostat, romidepsin, belinostat and panobinostat. The promising therapeutic value of HDACi is further substantiated by a growing number of clinical studies using these inhibitors. A recent search through clinicaltrials.gov revealed 613 clinical trials including HDACi, with 44 of these clinical trials focused on the effects of HDACi in combination with radiation therapy. Results from these ongoing studies will help elucidate optimal treatment combinations and dosing regimens for various types of cancers such as breast cancer, pancreatic cancer, brain tumors and hematopoietic malignancies. Moreover, these clinical trials, along with new insights from basic scientific research focused on determining which HDACs are most involved in the radio sensitivity of cancerous cell lines, will aid development of more effective HDACi to increase radiotherapy success. In parallel, development of reliable cellular and molecular biomarkers to determine which patients would benefit most from HDACi drug incorporation would greatly increase the viability, specificity, and value of this combinatorial therapeutic approach.

Looking Towards the Future

The vast majority of existing HDACi function against three families of human HDACs: class I, II and IV [16]. Yet, exploration into the role and potential promise of a whole other HDAC family, class III, which consists of seven members, sirtuins 1-7 [17], remains premature at best. Given the potential value that inhibitors of class I, II and IV HDAC have shown along with the huge expansion of sirtuin-focused research in recent years, it seems logical that therapeutic exploration of sirtuin-specific inhibition could yield equally encouraging results. Several sirtuin-specific inhibitors have been developed but with mixed results in both cellular systems and animal models [18,19]. This may be the result of the poorly understood role of sirtuins within cellular regulation or other functions such as signaling redundancy. Therefore, better knowledge of sirtuins' cellular and genetic context may be critical for the successful development of sirtuin-specific therapeutics. Regardless, what is certainly known is that members of the sirtuin family deacetylate substrates involved in DNA damage repair pathways. Studies have shown that SIRT1 and SIRT6 are recruited to DSBs and play key parts in both NHEJ and HR [20]. Sirtuin inhibition in this setting could sensitize cancerous cells to radiation in manners resembling the effects of existing HDACi. Based on ongoing HDAC research and the clinical promise that HDACi have shown when used in conjunction with existing radiotherapies, it is reasonable to suggest that the repertoire and therapeutic effectiveness of available inhibitors targeting histone deacetylases will increase in the near future.

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