INFECTIOUS AGENTS AND CANCER

LETTER TO THE EDITOR Open Access

Histone de-acetylase inhibitors: a promising future for cancer treatment?

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Histone de-acetylase proteins or lysine de-acetylases, represent a group of enzymes regulating DNA and gene expression by eliminating acetyl groups (de-acetylation) from lysine amino acids on histones and non-histone proteins [1,2]. Histone de-acetylase functions normally by being involved in a series of cellular pathways like cell growth, cell cycle, signal transduction, notch signaling pathway and especially transcription [3]. Although these functions allows histone de-acetylases to control expression of proteins involved in cancer initiation and cancer progression, abnormal acetylation of histone tails may occur with the resulting transcriptional lesions disrupting the apoptotic program of cells and leading to neoplasia [4,5]. To counter, development of antineoplastic agents called histone de-acetylase inhibitors (HDIs) have been introduced to interact with the catalytic site and blocking substrate access of histone de-acetylases in proliferation of tumor cells [6]. This anti-proliferative effect of HDIs in down regulation of BMI1 and c-MYC protein levels has shown promising results in treatment of the incurable AML as well as silencing estrogen receptor alpha in prevention of breast cancer [7,8].

The precise molecular actions of HDIs are unclear with epigenetic pathways the proposed mechanism [9].

HDIs mainly induce activation of both intrinsic and extrinsic apoptotic pathways of neoplastic cells by affecting protein stability, protein-protein interactions through interference with the function of cell cycle proteins such as p21, inhibition of signaling pathways implicated with Raf/MEK and activation of Reactive Oxygen Species [10,11]. In stress, HDIs acetylate DNA damage-response proteins, such as Ku70, causing the translocation of BAX to the mitochondria and activating apoptosis [12]. Recently they have been known to cause autophagy of signaling pathways like mTOR, AIF which is a major development [13]. Some studies have also shown HDIs contributing to growth suppression of primary tumors by enhancing tumor-cell's immunogenicity via transcriptional activation of MHC (1/2) proteins and suppression of tumor angiogenesis by inhibition of hypoxia-induced VEGF expression [14,15].

Despite the intrinsic anticancer potential, there are noteworthy limitations of these promising antineoplastic agents [11]. Combinations of HDIs with other cancer modalities such as anthracyclines have been found to be effective in pre-clinical and clinical evaluation; however, their additive effect has also led to potential complexities such as resistance to anthracycline (doxorubicin) in leukaemia cells and augmentation of cardiac toxicity [16]. Through modulation, HDIs also reactivate some latent viruses like human herpesvirus-6 predisposing to re-infection [17]. However, resistance to HDACi-induced transformed cell death, as observed in clinical trials of human bladder carcinoma cells and prostate cancer cells and non-specific action against a large group of Histone de-acetylases forms the major limitations of these agents [15]. Basis of this resistance is yet to be understood [15].

Regardless of the Food and Drug Administration (FDA) approval of Vorinostat (SAHA) and Romidepsin (ISTODAX) for the promising treatment of cutaneous T cell lymphoma, usage of HDIs as mono-therapies in other types of cancer has had moderate effects [18]. Pre-clinical studies on cancers have concluded better synergistic and additive effects of HDIs with combination of chemotherapeutic drugs by helping improve HDIs therapeutic index [18]. With complete and proper understanding of the major limitations of HDIs, their antitumor efficacy can be achieved enhancing the novel use of these anticancer drugs for the future treatments just like their current use as mood stabilizers and anti-epileptics.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
RSK: wrote article. HH: wrote article. RAB: made changes, proof read. ANK: idea and search, made revision changes. HR: made revision changes. All authors read and approved the final manuscript.

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