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Hydroxamic acid as anticancer agent

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ABSTRACT

Hydroxamic acids serve as a monsulfhydril bisubstrate analog inhibition of fernesyl protein transferase (FPT), the enzyme catalysing fernesylation of p^{21ras}. Tumor necrosis factor (TFN) is specifically prevented by synthetic hydroxamic acid-based metalloproteinase inhibitors. Suberoyanilide hydroxamic acid (SAHA) have been identified as histone deacetylase inhibitors based on their ability to induce differentiation of cultured murine erytholeukemia cells.

Key words: Hydroxamic acid, anticancer agent.

INTRODUCTION

In most organs and tissues of mature animal, a balance is maintained between cell renewal and cell death. The various types of nature cells in the body have a given life span; as these cells die, new cells are generated by proliferation and differentiation of various stem cells. Under normal circumstances, the production of new cells is regulated so that the number of any particular of new cells remains constant. Occasionally, though cells arise that no longer respond to normal growth control mechanism. These cells give rise to clones of cells that can, expand to a considerable size, producing a tumor or neoplasm[1-2].

A tumor that is not capable of indefinite growth and does not invade the healthy surrounding tissue extensively is benign. A tumor that continues to grow and becomes progressively invasive is malignant. The terms cancer refers specifically to a malignant tumor. In addition to uncontrolled growth, malignant tumors exhibit metastasis. In this process, small clusters of cancerous cells dislodge from a tumor, invade the blood and are carried to other tissues, where they continue to proliferate. In this way a primary tumor at one site can give to a secondary tumor at another site.

Cancers are classified according to the embryonic origin of the tissues from which the tumor is derived. More than 80% are carcinomas, tumors that arise from endodermal or exodermal tissues such as skin or the epithelial lining of internal organs and glands. The majority of cancers of the colon, breast, prostate and lung are carcinomas. The leukemias and lymphomas are malignant tumors of hematopoietic cells of the bone narrow, sarcomas which arise less frequently, are derived from mesodermal connective tissues such as bone, fat, and cartilage.

The process of uncontrolled cellular proliferation and differentiation causing cancer is recognised to be triggered by two main pathways, namely, activation of cellular protooncogenes and inactivation of tumor-suppressor genes[3]. The most common and potent members in these two categories are ras oncogenies and p^{53} tumor suppressor genes[4], respectively, as evident by their frequent detection in a wide variety of human tumors. Intervention of the biological pathway leading to the oncogenic activity of the corresponding oncoproteins forms the basis for rational design of novel and specific 'anti-cancer' agents. To date, blockade or attenuation of the ras pathways has received most attention from the

medicinal community in their search for antitumor drugs. A prerequisite to the transforming activity of the cytosolic ras proteins is their localization to the plasma membrane, an event that is carried out by a well-defend sequence of post-translational modifications[5]. One approach for blocking the oncogenic ras activity would to be use specific inhibitors to interrupt the activity of any or more of the enzymes catalyzing these pose translation modifications. Most attention has been focused toward the design and synthesis of inhibitors of Farnesyl Protein Transferase (FPT), the enzyme catalyzing farnesylation of p21 ras[6]. The CAAX (C=Cysteine, A=aliphatic amino acid, X-serine of methionine) tetrapeptide sequence renders enough specificity for recognition by the enzyme, and various peptidomimetic variants of this motif have recently emerged as very novel and potent inhibitors of FPT. With the exception of the recently reported imidazole zinc chelator based compounds, a mandatory feature of almost all peptide-based inhibitors with good potency has been the presence of a cysteine like free mercaptan group. Recently a new class of FPT inhibitors would have been reported where sulfhydryl group has been replaced by a phosphinyl or carboxylic acid pharmacophore. These non-sulfhydryl inhibitors would also bypass toxicological and metabolic issues that may be specifically associated with a mercaptan moiety[7]. Patel *et al*., reported a new class of hydroxamic acid pharmacophore based, nonsulfhydryl bi-substrate analog inhibitors of FPT[8].

The hydroxamic group is expected to benefit from ionic chelation interaction prevailing at the active site of FPT during the farnesylation reaction. The fernesyl group of farnesyl pyrophosphate (FPP) and the tripeptide group of the C-terminal CAAX motif are anchored together via a hydroxamic acid-bearing linker. By introducing the hydroxamate group as a linear component of the linker instead of a branched functional group, the issue of additional chirality in that region of molecule is also avoided.

Tumor necrosis factor (TNF) is a cytokin which is produced initially as a cell-associated 28kD precursor[9]. It is released as an active, 17kD form, which can mediate a large number of deleterious effects in vivo. When administered to animals of humans is causes inflammation, fever, cardiovascular effects, haemorrhage, coagulation and acute phase responses, similar to those seen during acute infections and shock states. Chromic administration can also cause cachexia and anorexia.

There is considerable evidence from animal model studies that blocking the effects of TNF with specific antibodies can be beneficial in acute-infections, shock states, graft versus host reaction and autoimmune diseases. TNF is also an autocrine growth factor for same myclomas and lymphomas and can act to inhibit normal haematopoiesis in patients with these tumors. Compounds which inhibit the production or action of TNF are therefore thought to be potentially useful for the treatment or prophylaxis of many inflammatory, infections, immunological or malignant diseases.

Gorden *et al*., showed that the release of mature TNF-α from leukocytes cultured in vitro is specifically prevented by synthetic hydroxamic acid-based metalloproteinase inhibitors, which also prevent the release of TNF-α into the circulation of endotoxin challenged rates. A recombinant, truncated TNF-α precursor is cleaved to biologically active, mature TNF-α by several matrix metalloproteinase enzymes. These results indicate that processing of the TNF-α precursor is dependent on at least one matrix metalloproteinase-like enzyme, inhibitor of which represents a novel the therapeutic mechanism for interfering with TNF-à production.

Hydroxyurea (-CONHOH) containing group is a well known anti-cancer drug[11-13]. It inhibits the DNA synthesis by impairing the activity of enzyme ribonucleotide reductase. Though it is clinically used as anticancer agent, it perturbs the hematological parameters and depresses the bone narrow.

Recently is has been reported that chlorohydroxamic acid possesses antitumor properties and inhibits the growth of Ehrlich ascites carcinoma (EAC) cells by impairing DNA and protein synthesis without altering the hematological parameters[14]. In an another study benzohydroxamic acid was shown to have significant antitumor activity[15]. Substituted benzohydroxamic acid has

been prepared to enhance the effect of benzohydroxamic acid and its complexes with copper metal ions are used as a potential antitumor drug[16-18].

Histone deacetylases (HDACs) regulates histone acetylation by catalysing the removal of acetyl groups of the NH_2-terminal residues of the core nucleosomal histones. Modulation of the acetylating states of the core histones is involved in the regulation of the transcriptional activity of certain genes. HDAC activity is generally associated with transcriptional with the development of certain human cancer. A class of HDAC inhibitors such as suberoylanilide hydroxamic acid (SAHA) have been developed, that were initially identified based on their ability to induce differentiation of cultured murine erythroleukemia cells. SAHA is the prototype of a family of hybrid polar compounds that induce growth of assets in transformed cells and show promise for the treatment of cancer. SAHA induces differentiation and/or apopotosis in certain transformed cells in culture and is protect inhibitor of histone deacetylases. The effects of SAHA on the growth of the CWR 22 human prostate xenograft in nude mice have been studies[19]. The results suggest that hydroxamic acid-based hybrid polar compounds inhibit prostate cancer cell growth and may be useful, relatively, non-toxic agents for the treatment of prostate carcinoma.

In an another study the effects of SAHA on MCF-7 human breast cancer cells have been examined[20]. It is found that SAHA causes inhibition of proliferation and accumulation of cells in a dose dependent manner in G, then G_2-M phase of the cell cycle, and induction of milk fat globule protein, milk fat membrane globule protein, and lipid droplets. Growth inhibition was associated with morphological changes including the flattering and enlargement of the cytoplasm, and a decrease in the nucellar cytoplasmic ratio. Withdraw of SAHA led to recently of cells into the cell cycle and reversed to a less differentiated phenotype. It has been proposed that SAHA has profound antiproliferative activity by causing these cells to undergo cell cycle arrest and differentiation that is dependent on the presence of SAHA.HDAC activity is recruited by corepressor proteins to certain regions of the chromatin and aberrant histone acetylation caused by that recruitment is responsible for the pathogenesis of certain cancer on a molecular level. Inhibitors of HDAC have been identified in natural sources and also synthetic inhibitors are available. The best studied inhibitor is trichostatin A, a hydroxamic acid that exerts its activity by complexation of a zinc ion that is supposed to mediate the acetamide cleavage at the catalytic site[21]. First clinical studies have shown that histone hyperacetylation can be achieved safely in humans and that treatment of cancer is possible.

Pharmacokinetics and bioavailability of SAHA in the patients of cancer have also been studied. Patients with solid and hematologic malignancies were treated with SAHA, administered once or twice a day on a continuous basis or twice daily for 3 condsecutive days per weak. Pharmacokinetic profile and bioavailability of oral SAHA were determined. Oral SAHA has a linear pharmacokinetics and good bioavailability, inhibits HDAC activity in peripheral blood mono-nuclear cells, can be safely administered chronically and as a wide range of anti-tumor activity[22]. In addition to their intrinsic anticancer properties numerous studies have demonstrated that HDAC inhibitor can modulate cellular responses to their cytotoxic modalities including ionising radiation, ultraviolet radiation and chemotherapeutic drugs[23].

SAHA can cause growth arrest and death of a broad variety of transformed cells both in vitro and in vivo at concentrations that have little or no toxic effects on normal cells. It inhibits the activity of HDACs, including all 11 known human class I and class II HDACs. SAHA has significant anticancer activity against both hematologic and solid tumors at doses and well tolerated by patients. A new drug application has been approved for SAHA treatment of cutaneous T-cell lymphoma[24].

Hydroxylurea has been used for decades and it is still valuable for the treatment of some types of cancer[11-13]. It inhibits ribonucleotide reductase (RNR) enzyme known to be crucial in the conversion of ribonueleotides into deoxyribonucleotides. However, now a days main focus has been shifted to structurally similar hydroxamic acid derivatives that target specific enzymes involved in cancer progression such as HDACs, matrix

metalloproteinases and also RNR[25]. The biochemists working in this area are actively engaged in synthesizing such hydroxamic acids with anticancer activity.

By employing an intramolecular Pd (O)-mediated ring opening of an acylnitroso derived cycloadduct, new hydroxamic acid containing benzodiazapines have been synthesized and have demonstrated biological activity in MCF - 7 & PC - 3 tumor cell lines[26].

At present, a group of researchers are engaged in investigating the additive and synergistic effect of combined treatment of a HDAC inhibitor like SAHA and some other anticancer agent like Erlotinib. The result is found encouraging if these drugs are administered in the therapeutically effective amounts.

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