Discovery of Selective Vitamin D Receptor Coregulator Inhibitor

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Abstract
Vitamin D Receptor (VDR) is known to be involved in calcium homeostasis and recently, for its role in cell growth and differentiation. Here, we present the research highlight for discovery of selective inhibitor which blocks the interactions between VDR and co-regulators. This review discusses the anti-cancer effect of lead inhibitors in cancer cell-lines and its role in regulation of various VDR related genes.

Keywords: anti-cancer, calcitriol, HL-60**,** vitamin D receptor

Introduction

Vitamin D receptor (VDR) belongs to a family of nuclear receptors and has been long known for its crucial role in calcium homeostasis. Recently, the role of VDR in cell growth and cell-proliferation was reported [1]. In cell, the inactive form VDR is bound to a co-repressor.Upon binding with its ligand, VDR undergoes conformational changes that lead to binding with a co-activator [2]. Upon activation, VDR binds with retinoid X Receptor to form heterodimer that binds with DNA response element on genome to transcribe the related gene. VDR is ubiquitously present in tissues but plays a very selective and tissue-specific role. This selective function of VDR is due to binding with a specific coactivator.

Calcitriol, active form of vitamin D, is a natural ligand of VDR [3]. Recently, Calcitriol was evaluated for its anti-cancer properties in clinical trials. However, due to significant hypercalcemia caused by disturbing the calcium metabolism, the trial was withdrawn [4]. Later, a number of calcitriol derivatives were synthesized and assessed for anti-cancer properties. Tremendous efforts were made to synthesize a molecule that has low calcemic properties [5]. Another approach for inhibiting VDR was to selectively inhibit the interaction between VDR and its coactivators. Very few molecules were designed that could selectively inhibit the VDR-coactivators interaction. One of the major advantages of this approach is specific inhibition of proliferative function of VDR withoutdisturbing calcium homeostasis [6-9].

Discussion

In this research highlight, one approach of selectively inhibiting the interactions of VDR and its coactivator SRC2-3 is discussed [10, 11]. Initial lead molecule was discovered from high throughput screening. Several compounds were screened to identify a molecule that can inhibit the interaction between VDR and SRC2-3. Basedon this screening, a class of molecules having indole scaffold were selected for structure activity studies. The synthesis of indole scaffold was achieved in one step using microwave-based aza-indole reaction. A library of molecules was readily synthesized by making variations at various positions on indole ring. The molecules were evaluated using primary fluorescent assay using purified VDR-LBD and fluorescent-labelled SRC2-3 peptide to inhibit the interactions between VDR and SRC2-3. In secondary cell-based transcription inhibition assay, HEK293T cells were transfected VDR-LBD plasmid and luciferase-VDRE plasmid and potency of molecules to inhibit the transcription of VDR to form luciferase was evaluated. Physiochemical parameters such as solubility, permeability and toxicity were also

measured. Based on these results, lead molecule PS121912 was identified for further evaluation for its anti-cancer properties.

In order to assess the selectivity of lead molecule, it was evaluated against a panel of other nuclear receptors and various co-activators. It was found that PS121912 was very selective of VDR and SRC2-3. To evaluate the anti-cancer properties of PS121912, toxicity and viability of HL-60 cancer cells was measured by incubating with different concentrations of PS121912. Also, the ability of PS121912 to initiateapoptosis in HL-60 cancer cells was assessed. It was found that this compound significantly caused apoptosis at very low concentration. It was also found that PS12912 reduced the transcription of CYP24A1 and CAMP genes at a concentration of 0.5 µM. Based on these data, it can be concluded that PS121912 inhibits transcription in a very selective manner to induceapoptosis in cancer cells.

The discovery of selective inhibitors of VDR having anti-cancer properties but devoid of calcium related side effects is very important. Most of the secosteriod-based inhibitors of VDR are associated with hypercalcemia thereby, dampening the clinical success. This work contributes to a big step toward the discovery of very potent and selective inhibitors of VDR. However, clinical potential of these inhibitors is yet to be determined.

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