Personalized Medicine Universe 4 (2015) 23–26

Contents lists available at ScienceDirect

Personalized Medicine Universe

journal homepage: www.elsevier.com/locate/pmu

Review

Repositioned alpha-1 adrenoceptor blockers as anti-tumor drugs

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ARTICLE INFO

Article history:
Received 20 March 2015
Accepted 10 April 2015

keywords:
Drug development
Drug repositioning
Anti-tumor drug
Alpha-1 adrenoceptor blocker
Apoptosis

ABSTRACT

Purpose: Drug development has often occurred serendipitously, rather than by using rational approaches. Drug repositioning is an approach that can exploit serendipitous features of a licensed drug.
Study selection and results: Drug repositioning has mainly been used to develop anti-tumor drugs. There are two approaches, drug-based and non-drug-based. The drug-based method develops new drugs using information related to drug function, cohort studies, or side effects. This approach identified anti-tumor drugs, including alpha-1 blockers, HIV-1 protease inhibitors, and metformin. On the other hand, the non-drug-based approach aims to identify drugs using drug libraries and an appropriate assay for each disease. This approach is similar to traditional drug development methods.
Discussions and conclusions: Drug repositioning approaches have enabled our group and others to identify novel anti-tumor drugs. Therefore, drug repositioning can be useful in the development of promising anticancer therapies.

1. Purpose

Drug repositioning is attracting worldwide attention as a strategy for drug development using the large number of existing drugs. Current pharmaceutical drug development approaches are limited by their inefficiency [1,2]. Research and development efforts are expensive and require a long time to reach the completion of Phase III drug discovery trials. The drug repositioning approach is less expensive and more rapid, two major advantages for identifying new chemical entities relevant to drug discovery. This is because repositioned drugs have established synthetic methods, well-defined pharmacokinetics and side-effects, and have passed the required toxicity and safety tests. In other words, all the necessary information is available for repositioned drugs, with the exception of their efficacy for other applications. Over 10 drugs have already been relicensed as repositioned drugs [3]. Many other drugs have been reported as candidates for repositioning [4–6]. Over ten candidate drugs have been identified within the cancer therapy field. This review introduces some examples of successful drug development using the drug repositioning approach.

2. Study selection and results

2.1. Repositioned drugs as ethical pharmaceuticals

One of the most successful repositioned drugs is sildenafil (Viagra: Pfizer), which is used to treat erectile dysfunction. Sildenafil is an inhibitor of cyclic guanosine monophosphate hydrolysis, catalyzed by a type 5 phosphodiesterase. The first clinical trials of sildenafil were not for erectile dysfunction, but for angina. These trials were unsuccessful, but some subjects reported improvement of erectile dysfunction as one of the treatment side effects [7–9]. Using this serendipitous finding, Pfizer switched direction and developed sildenafil as a drug for erectile dysfunction, rather than for angina [10].

Another highly successful repositioned drug is allopurinol (Zyloric: GlaxoSmithKline). Allopurinol is an inhibitor of the oxidation of hypoxanthine, catalyzed by xanthine oxidase. Allopurinol was designed to inhibit uric acid production from its immediate precursors, hypoxanthine and xanthine [11]. This can be used to treat hyperuricemia, which is associated with gout, urolithiasis, and renal insufficiency [12]. Allopurinol was originally developed as a suppressor of hyperuricemia in the treatment of leukemia [13]. The observed reduction of uric acid in serum and

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http://dx.doi.org/10.1016/j.pmu.2015.04.003

urine of patients receiving allopurinol led to its usage in gout treatment [14].

2.2. Drug repositioning methods

The route to drug development varies for each repositioned drug. However, drug repositioning methods can be classified as either drug-based or non-drug-based. The drug-based drug repositioning approach uses information about side effects or off-target effects, reported in public databases and observational cohort studies, to identify the relevance of a drug for a different target disease. This approach can be successful because a potential target disease can be predicted from drug information that has been compiled for over half a century, in line with advances in digitization and computational science. This method was utilized to find repositioned drugs such as sildenafil and allopurinol [9,14]. However, it is hard to utilize drug-based repositioning in the absence of any information about the connection between a disease and a drug. In contrast, non-drug-based drug repositioning does not require this information, but instead utilizes a disease-related assay system and a drug library. This is similar to traditional drug development methods, except that licensed drugs are tested, rather than novel compounds. Depending on the information and assay systems available, one of these methods is selected as a first step in drug repositioning.

2.3. Repositioned anti-tumor drugs under development

Metformin (Metgluco: Dainippon Sumitomo Pharma) is a well-known oral anti-diabetic drug with clinical experience dating back to 1962 in Japan and other countries [15–17]. The mechanism underlying metformin's anti-diabetic activity was unknown for a long time; however, Zhou et al. have reported that metformin activates AMP-activated protein kinase (AMPK), which inhibits mammalian target of rapamycin (mTOR) in the Akt pathway [18]. Moreover, the therapeutic effect of metformin relates to glucose homeostasis mediated by liver kinase B1 (LKB1) in the liver [19]. Recent cohort studies suggested that metformin may decrease the cancer risk of diabetic patients [20,21]. A high level of metformin was shown to suppress the growth of multiple cancer cell types [22–28].

The clinical treatment of HIV patients uses specific HIV-1 protease inhibitors such as indinavir (Crixivan: Merck), nelfinavir (Viracept: Japan Tobacco), ritonavir (Norvir: AbbVie), and saquinavir (Fortovase: Roche). These inhibitors are associated with the catalytic region of HIV-1 protease [29,30]. This region is structurally similar to cytoplasmic retinoic-acid binding proteins (CRABPs), which also bind HIV-1 protease inhibitors [31]. This binding inhibits cell proliferation in acute promyelocytic leukemia (APL) cells [32]. HIV-1 protease inhibitors also induced cell death in human breast cancer, glioblastoma, Kaposi's sarcoma, lung cancer, multiple myeloma, pancreatic cancer, and prostate cancer [33–36].

Piperlongumine (PL), an alkaloid found in *Piper longum*, acts as an anti-tumor drug against different types of cancer cells, enhancing reactive oxygen species (ROS) accumulation. PL was identified as anti-tumor drug using the screening by p53 response by ROS [37]. PL downregulated NF-kappa B activity in malignant B-lymphoma cells and prostate cancer cells [38,39]. Exposure of HT-29 cells, a colon cancer cell line, to PL induced activation of extracellular signal-regulated kinases (ERK) via mitogen-activated protein kinase (MAPK)/ERK kinase (MEK) activation [40]. Glioblastoma multiforme cells were selectively killed by PL-dependent p38 activation [41]. PL promotes autophagy via inhibition of Akt/mTOR signaling in different types of cancer cells, including prostate cancer cells, breast cancer cells, and renal carcinoma cells [42].

2.4. Direct anti-tumor effects of alpha-1 blockers

Alpha-1 blockers have been used to treat hypertension and benign prostatic hyperplasia (BPH) [43–48]. Some selective alpha-1 blockers, including alfuzosin, doxazosin, naftopidil, prazosin, tamsulosin, and terazosin, have been used to treat BPH [49–51].

Doxazosin, one of the quinazoline-based alpha-1 blockers used for BPH, induces apoptosis in the mouse prostate reconstitution model. This result suggested that the apoptosis induced by doxazosin contributed to the alleviation of urination disorders in men with BPH [52]. This study started to investigate alpha-1 blockers as inducers of cell death. The Kyprianou group reported that doxazosin and another quinazoline-based alpha-1 blocker, terazosin, induced apoptosis in prostatic epithelial and stromal cells of BPH patients [53,54]. Both drugs, but not the alpha-1 blocker, tamsulosin, induced these effects via poly ADP ribose polymerase (PARP) activation; doxazosin also suppressed a PC-3 human prostate cancer tumor in the xenograft mouse model, via an alpha-1-independent effect [55,56]. In addition to prostate cancer, doxazosin induces cell death in bladder cancer, breast cancer, glioblastoma, ovarian cancer, and renal cell carcinoma [57–61]. Doxazosin-induced apoptosis in human prostatic stromal cells is regulated via transforming growth factor (TGF)-beta signaling and I kappa B alpha induction [62,63]. Doxazosin and terazosin induce anoikis and inhibit prostate cancer cell invasion via the suppression of bcl-2; this induces down-regulation of vascular endothelial growth factor (VEGF) mRNA [64]. In human ovarian cancer cells, doxazosin treatment suppresses VEGF receptor phosphorylation and downstream signaling via Phosphoinositide 3-kinase (PI3K), phosphoinositide-dependent kinase (PDK)-1, Akt, and mTOR [60]. DNA microarray analysis of LNCaP cells showed that doxazosin induced apoptosis via the down-regulation of DNA replication-related genes, including Growth arrest and DNA-damage-inducible protein 45 (GADD45A), X-ray repair cross-complementing protein 5 (XRCC5), and protein kinase, DNA-activated, catalytic polypeptide (PRKDC) [65]. It was recently reported that prazosin, another quinazoline-derived alpha-1 blocker, induced apoptosis in human prostate cancer cells with greater potency than doxazosin; prazosin targeted DNA damage-related stress and induced cell cycle arrest at the G2 checkpoint [66]. Prazosin reduced the viability of human bladder cancer cells, erythroleukemia cells, renal cell carcinoma, and thyroid carcinoma cells [67–69]. More recently, naftopidil was found to inhibit prostate cancer and renal cell carcinoma growth by inducing G1 arrest *in vitro* and *in vivo* [70,71]. In bladder cancer, we found that naftopidil suppressed cell growth by acting via the caspase-3 pathway (Nakagawa et al., unpublished data). Naftopidil induced G1 arrest via the up-regulation of p21 and/or p27, and also blocked smad2 phosphorylation via TGF-beta activation in prostate cancer [71]. The HUHS series of naftopidil-derived analogues reduced cell viability in human bladder cancer, gastric cancer, liver cancer, lung cancer, malignant mesothelioma, prostate cancer, and renal cell carcinoma *in vitro* [72]. One of this series, HUHS1015, was found to inhibit human gastric cancer and malignant mesothelioma [73,74].

2.5. Indirect anti-tumor effects of alpha-1 blockers

The inhibition of angiogenesis is a cancer therapy target because many tumors require a plentiful supply of glucose, lipids, and amino acids from the blood. Angiogenesis is promoted by VEGF and its receptor, which has thus attracted attention as an anti-tumor drug development target. VEGF-induced endothelial cell proliferation and migration promote the formation of new blood vessels to supply tumors [75,76]. Doxazosin was shown to decrease prostate tumor vascularity in a clinical sample by decreasing VEGF