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Identification and characterization of the druggable kinase targets of olmesartan and its analogues from a systematic kinase–chemical interaction profile in atherosclerosis

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ABSTRACT

Olmesartan (OL) is the pharmacologically active metabolite of Olmesartan medoxomil (OM), an FDA-approved angiotensin II receptor antagonist for administrating cardiovascular diseases. The drug has been found to have potential effects on diverse protein kinase signaling involved in the pathogenesis of atherosclerosis, either by directly inhibiting the hub kinases or by indirectly modulating marginal members in the signaling pathways. In the present study, we computationally model the kinase–chemical Interaction Profile between six OL-related chemicals (*i.e.* OL, OM, Valsartan [VL], Losartan [LS], Candesartan [CD] and Telmisartan [TL]) and 23 human protein kinases in atherosclerosis. The profile is analyzed systematically at molecular level to identify unexpected kinase targets for OL. There is a good consistence between co-citation frequency and affinity scoring for the chemical association with kinase candidates; the OL and its analogs VL and LS exhibit a similar binding profile to the atherosclerosis kinase spectrum. It is suggested that the Ser/Thr-specific kinases PI3Kα and ROCK1 are potential druggable targets of OL for atherosclerosis therapy. As a paradigm, kinase assays reveal that the inhibitory potency of OL and Y-27632 (positive control) on ROCK1 is determined at micromolar level, while the OM (negative control) possesses no detectable activity for the kinase.

1. Introduction

Atherosclerosis is a progressive disease characterized by the accumulation of lipids and fibrous elements in the large arteries. The early lesions of atherosclerosis consist of subendothelial accumulations of cholesterol-engorged macrophages termed as 'foam cells' [1]. A persistent increase in circulating low-density lipoprotein (LDL) levels in the body is one of the most important causes for the initiation and progression of atherosclerosis. Macrophages play an essential role by increasing accumulation of lipids in blood vessels, leading to inflammation and plaque formation [2]. Several biochemical pathways are involved in the development of atherosclerosis that would be possible targets for improving strategies for disease diagnosis and management. Earlier anti-inflammatory or lipid-lowering treatments could be useful for alleviating morbidity and mortality of atherosclerotic cardiovascular diseases. However, novel drug targets like endoglin receptor, squalene synthase, PPAR family proteins and thyroid hormone analogues are more powerful to control the process of atherosclerosis [3].

Olmesartan medoxomil (OM) is an angiotensin II type 1 receptor antagonist that inhibits the actions of angiotensin II on the renin-angiotensin-aldosterone system (RAAS) that plays a key role in cardiovascular diseases [4]. The OM is a prodrug that has a variety of *in vivo* metabolites including the pharmacologically active Olmesartan (OL) [5], showing a complicated interaction profile with human proteins. In recent years, it has been found that the OL (or OM) exhibits potential effects on diverse protein kinase signaling such as MAPK, AMPK and ROCK that are closely related to atherosclerosis, either by directly inhibiting the hub kinases or by indirectly modulating marginal members in the signaling pathways [6,7].

Although there is a significant relationship between the atherosclerosis pathogenesis and OL–kinase interaction, the underlying molecular mechanism and biological implication still remain largely unexplored. It is supposed that the pharmacological effect of OL on atherosclerosis is acted by targeting unexpectedly certain functional kinases in cardiovascular system; the OL-meditated pharmacological effect may not be achieved effectively by the binding of OL to only one or few kinases due to the complex-

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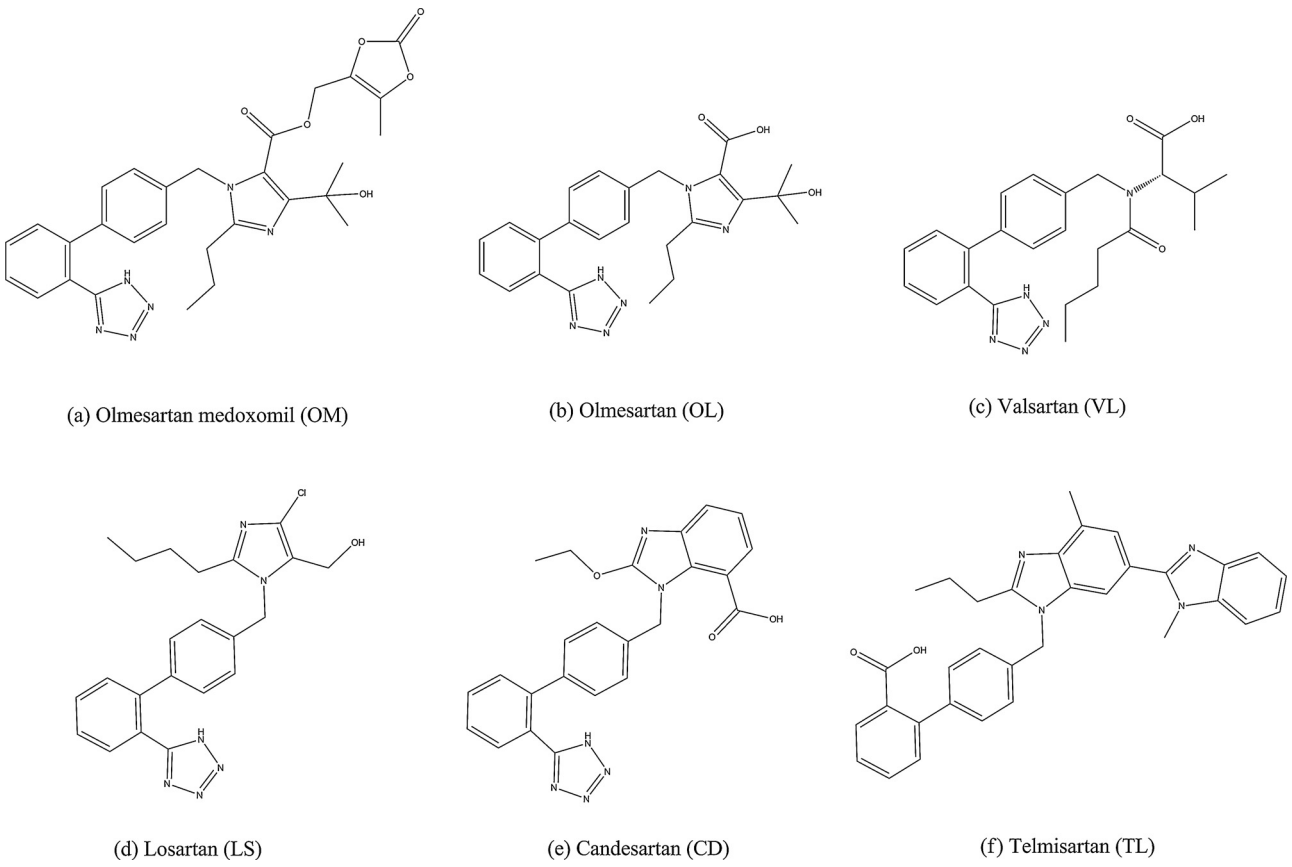

Fig 1. Chemical structures of Olmesartan medoxomil (OM) (a), Olmesartan (OL) (b), Valsartan (VL) (c), Losartan (LS) (d), Candesartan (CD) (e) and Telmisartan (TL) (f).

ity of atherosclerosis pathogenesis, and multiple targets would be expected in the atherosclerosis-related OL–kinase interaction. Previously, Jiang and co-workers successfully identified the druggable interactions between human protein kinases and naturally occurring compounds in endometriosis by using a gene ontology (GO)-based strategy [8]. Here, a systematic interaction profile for atherosclerosis-related protein kinases against OL as well as OM and some other chemical analogs (termed as chemicals) was computationally modeled with the GO strategy as well as high-throughput cross-docking and scoring. The kinase–chemical interaction profile was also analyzed by integrating computational modeling and kinase assay to understand the molecular mechanism and biological implication underlying the kinase–drug interaction in atherosclerosis.

2. Materials and methods

2.1. Chemical collection

Olmesartan medoxomil (OM) (Fig. 1a) is an angiotensin II receptor blocker that was originally approved by U.S. FDA for the treatment of high blood pressure [4]. Orally administered OM was rapidly absorbed from the gastrointestinal tract and converted during absorption to Olmesartan (OL) (Fig. 1b), the pharmacologically active metabolite that was subsequently excreted without further metabolism [8]. The OL has recently been found as a potential mediator of diverse protein kinase signaling in atherosclerosis [6,7]. In addition, four chemical analogs, namely Valsartan (VL), Losartan (LS), Candesartan (CD) and Telmisartan (TL) (Fig. 1c–f, respectively), were compiled as controls. The four drug compounds are also angiotensin-receptor blockers and are structurally similar to OL and OM, but they have no reports or have only been limitedly related to atherosclerosis.

2.2. Structural analysis, molecular docking, dynamics simulation, and affinity scoring

2.2.1. Homology modeling

Three-dimensional structures of the collected co-cited kinases (see Table 1) were either retrieved from the PDB database [9] or predicted *via* homology modeling [10]. For the latter, the homologous protein templates of target kinases were determined by sequence search; the sequence identity between target and template should be >30%. In the procedure the target kinases were built using Modeller9v4 program [11] based on the crystal structure of template proteins. The method grafted identical regions from template to structure model and then used a loop optimization algorithm to implement *ab initio* prediction of loop regions of the model.

2.2.2. Molecular docking

The hydrogen atoms and protonation state were assigned for the kinase proteins using REDUCE [12] and H++ [13] programs, respectively. Then, the atoms of protein receptors and ligand molecules were assigned with empirical partial charges, respectively. Protein structures and compound ligands were prepared for docking using AutoDockTools [14] with default settings. Molecular docking was performed using AutoDock [15], which used Lamarckian genetic algorithm (LGA) to explore ligand conformational space in the active site of kinase receptors [16].

2.2.3. Binding affinity calculation

The interaction affinity for each docked kinase–compound complex was calculated using molecular mechanics/generalized Born