Discoidin Domain Receptor

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Contributor: Kyeong Lee

Discoidin domain receptor (DDR) is a collagen-activated receptor tyrosine kinase that plays critical roles in regulating essential cellular processes such as morphogenesis, differentiation, proliferation, adhesion, migration, invasion, and matrix remodeling. As a result, DDR dysregulation has been attributed to a variety of human cancer disorders, for instance, non-small-cell lung carcinoma (NSCLC), ovarian cancer, glioblastoma, and breast cancer, in addition to some inflammatory and neurodegenerative disorders. Since the target identification in the early 1990s to date, a lot of efforts have been devoted to the development of DDR inhibitors.

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1. Introduction

Discoidin domain receptor (DDR), discovered in the early 1990s, belongs to a family of the transmembrane receptor tyrosine kinases (RTKs) which acts as a hub for signal transduction initiation. A discoidin motif (DS) which encompasses the collagen-binding site is a specific structural feature that distinguishes the human DDRs (DDR1 (CD167a) and DDR2 (CD167b)) from other RTKs. While DDR1 has five isoforms (DDR1a, DDR1b, DDR1c, DDR1d, and DDR1e) different in the extent of glycosylation, protein interactions, expression patterns, phosphorylation, as well as functions, DDR2 has only a single isoform to date. DDR1a, b, and c are found to be kinase-active, while DDR1d and e are kinase domain-deficient receptors with unknown function. It is well-established that ligands of typical RTKs are peptide-like growth factors, on the other hand, DDR activation is controlled by numerous types of triple-helical collagens. DDR1 is mainly expressed in epithelial cells of different tissues while DDR2 is found in mesenchymal cells including fibroblasts, myofibroblasts, smooth muscle cells, and chondrocytes. DDR plays a key role in the production and degradation processes of collagen and the essential cellular processes such as proliferation, differentiation, adhesion, in addition to matrix remodeling [1][2][3].

Collective evidence suggests that dysregulation of DDR is attributed to different human disorders, such as cancer, fibrosis, atherosclerosis, neurodegeneration, and other inflammatory disorders. Accordingly, DDR has been considered as novel potential molecular target, mainly for drug development of cancer. Many DDR inhibitors have been disclosed highlighting the promising potential of DDR inhibition as a novel therapeutic strategy [4][5]. From a medicinal chemistry perspective, this review offers an updated overview on the development journey of the most promising DDR small molecule inhibitors including design, structure-activity relationship (SAR), biological activity, and selectivity.

2. Biological Role of DDR

Both DDR1 and DDR2 are essential regulatory factors for organ development and physiological function [6][7][8][9][10][11]. In addition to their important roles in cell proliferation and differentiation, DDRs were also found to have rules in cell migration, invasion, and adhesion [12][13][14][15]. DDR1 has an essential role in the biogenesis of multiple organs, for example, DDR1-knockout mice were found to be shorter than their littermates and to have a lactational defect in pregnant females. Multiple reproductive disorders, including infertility due to abnormal embryo implantation and abnormal mammary gland growth, were also discovered in DDR1-null mice [16][17]. In addition to extreme auditory function loss and progressive morphological changes, they displayed abnormalities in kidney and inner ear architecture [18]. DDR1 deficiency impairs adhesion and migration abilities [19]; it was reported that DDR1a is an important factor for the promotion of leukocyte migration in three-dimensional collagen lattices [14]. DDR1 mediated activated T cells were also found to bind to collagen, which enhanced T cell migration [20].

DDR2 was reported to be involved in skeletetogenesis since it was found to be important for chondrocyte proliferation [21][22]; In DDR2-null mice, skeletal disorders such as the shortening of long bones and abnormal growth of flat bones have recently been reported [23]. Another study by Kano et al., showed the critical role of DDR2 signaling in the maintenance of male spermatogenesis [24]. Skin wound-healing disorders were also observed in DDR2-knockout mice, which were primarily caused by decreased skin fibroblast proliferation and abnormal extracellular matrix remodeling [15]. Furthermore, a link has been found between DDR2 deletion or mis-sense mutation and autosomal recessive growth disorders such as Smallie (Slie) and human spondylo-meta-epiphyseal dysplasia, which is characterized by short limbs and irregular calcifications (SMED-SL) [25][26][27][28][29]. Overexpression of DDR2 promotes the proliferation and invasion of hepatic stellate cells mediated by matrix metalloproteinase-2 (MMP-2) [30]. It was confirmed that DDR2 is necessary for normal fibroblast spreading and migration, regardless of the presence of adhesion ligands or collagen activation [31]. Studies also suggested that DDR2 function is essential for the membrane dynamics that control the mechanical attachment of fibroblasts to the 3D collagen matrices [32]. DDR2 reduction was also found to increase the population of CD8+ T cells as well as the sensitivity to anti–programmed cell death protein 1 (PD-1) therapy [33].

3. Conclusions

The available molecular docking studies allowed us to predict that a potent DDR1 inhibitor must contain certain structural features. One such essential structural feature is an amide linker that facilitates the formation of a hydrogen bond with GLU672 and an additional hydrogen bond with the backbone NH of ASP784. A moiety able to form hydrogen bonding with the “gate keeper” amino acid THR071 is another essential feature a potent and selective DDR1 inhibitor must possess. The ability of the synthesized compound to form a hydrogen bonding with MET704 as well as containing a hydrophobic moiety in its “tail” are two structural features that are predicted to further increase the binding affinity of any synthesized molecule with the DDR1 active site residue.

In addition to the classical methods of drug design, many researchers are currently attempting to apply new strategies to develop DDR inhibitors; for instance, ligand-based pharmacophore mapping [34], integrative

transcriptome meta-analysis [35], and deep learning [36][37][38][39]. However, given the fact that the pathological roles of DDR1 and DDR2 are not yet fully understood, further chemical biology research is highly needed to gain further understanding of these vital kinase targets. As discussed, several potent small molecule inhibitors were found in literature, for example, compounds **34**, **39**, and **40** (IC_{50} < 5 nM), however, major concerns related to selectivity, PK properties, mutation resistance, and safety of the promising inhibitors needs to be addressed. Since no selective DDR1 or DDR2 inhibitor has been moved into clinical investigation to date, we believe that further medicinal chemistry research aiming at SAR improvement of the most promising compounds highlighted in this review as well as design of DDR1 and DDR2 allosteric modulators targeting pockets out of DDR conserved kinase domain may play a significant role to develop more potent, selective, and safe inhibitors. Furthermore, since many of the discussed small molecule DDR inhibitors were found to share the same “skeleton”, a 3D QSAR study utilizing their known IC_{50} values would be key to the synthesis of new structurally modified DDR inhibitors with higher selectivity and potency.

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