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Review article

Recent advances in the development of dual VEGFR and c-Met small molecule inhibitors as anticancer drugs

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ABSTRACT

Vascular endothelial growth factor receptor (VEGFR) is a very important receptor tyrosine kinase (RTK) that can induce angiogenesis, increase cell growth and metastasis, reduce apoptosis, alter cytoskeletal function, and affect other biologic changes. Moreover, it is identified to be deregulated in varieties of human cancers. Therefore, VEGFR turn out to be a remarkable target of significant types of anticancer drugs in clinical trials. On the other side, c-Met is the receptor of hepatocyte growth factor (HGF) and a receptor tyrosine kinase. Previous studies have shown that c-Met elicits many different signaling pathways mediating cell proliferation, migration, differentiation, and survival. Furthermore, the correlation between aberrant signaling of the HGF/c-Met pathway and aggressive tumor growth, poor prognosis in cancer patients has been established. Recent reports had shown that c-Met/HGF and VEGFR/VEGF (vascular endothelial growth factor) can act synergistically in the progression of many diseases. They were also found to be over expressed in many human cancers. Thus, in a variety of malignancies, VEGFR and c-Met receptor tyrosine kinases have acted as therapeutic targets. With the development of molecular biology techniques, further understanding of the human tumor disease pathogenesis and interrelated signaling pathways known to tumor cells, using a single target inhibitors have been difficult to achieve the desired therapeutic effect. At this point, with respect to the combination of two inhibitors, a single compound which is able to inhibit both VEGFR and c-Met may put forward the advantage of raising anticancer activity. With the strong interest in these compounds, this review represents a renewal of previous works on the development of dual VEGFR and c-Met small molecule inhibitors as novel anticancer agents. Newly collection derivatives have been mainly describing in their biological profiles and chemical structures.

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1. Introduction

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body [1]. In 2012 about 14.1 million new cases of cancer occurred globally (not including skin cancer other than melanoma) [6]. It caused about 8.2 million deaths or 14.6% of all human deaths [2]. The financial costs of cancer have been estimated at $1.16 trillion US dollars per year as of 2010. Therefore, the development of the identification of novelly biological targets and the discovery of more specific chemotherapeutics are important objectives of current's research, especially for the most aggressive tumors. Cancer disturbs the normal cellular activities, namely, growth, differentiation, programmed cell death, and tissue integrity Among these growth factors, vascular endothelial growth factor (VEGF), which are crucial for the development and the maintenance of multicellular organisms [3]. With the rapid development of cell biology, molecular biology, genomics and proteomics, the targets of anticancer drug research has shifted to a new and more selective target for cancer cell proliferation, such as cancer cell signal transduction-pathways, growth factors and their receptors, apoptosis pathway, etc [4]. A promising therapeutic strategy for tumor is to inhibit tumor growth and angiogenesis by targeting key growth factor receptors [5]. Cellular signal transduction pathways play an important part in the process of tumor growth and angiogenesis [6,7].

The targeting of oncogenic protein tyrosine kinase signal transduction pathways in cancer cells is a very effective way to therapeutics in the molecularly targeted approach [8]. Receptor tyrosine kinases (RTKs), the high-affinity cell surface receptors for many polypeptide cytokines, hormones and growth factors, consist of 58 encode receptor tyrosine kinase proteins and 90 unique tyrosine kinase genes identified in the human genome [9]. Receptor tyrosine kinases are key regulators of normal cellular processes which have a critical role in the development and progression of many types of cancer. RPTKs that are both receptors and enzymes bind ligands with the target protein tyrosine residue phosphorylation [10]. This binding causes receptor tyrosine kinases (RTKs) at the extracellular domain. These enzymes play an important role in regulating intracellular initiation and relaying of growth and proliferation signals [11]. Studies have shown that RTKs contain a great number of growth factors and their receptors. For example, vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor (VEGFR); hepatocyte growth factor (HGF)/c-Met; nerve growth factor (NGF)/nerve growth factor receptor (NGFR); platelet-derived growth factor (PDGF)/platelet-derived growth factor receptor (PDGFR); fibroblast growth factor (FGF)/fibroblast growth factor receptor (FGFR) [12–14]. The activating mutations and/or overexpression of growth factors and receptors of them in signal transduction pathways, as well as other tyrosine factors and kinases, have been implicated in a variety of important human cancers including ovarian, brain, breast, non-small cell lung cancers, etc. [15], these strategies are strongly proved to be novel molecular targets of tumor therapy [16–26]. Among these growth factors and their receptors, VEGFR and c-Met receptor tyrosine kinase which appear to be important therapeutic targets of cancers, also have a remarkable biochemical and biological effect on cancer cells [20,22,27].

2. VEGF and its receptor VEGFR

In the 1960s, Folkman [28] proposed that tumor growth was angiogenesis dependent, and confirmed the close relationship between angiogenesis and tumor metastasis so as to death through experiment. Angiogenesis is regulated by many growth factors. Among these growth factors, vascular endothelial growth factor (VEGF) is the strongest and the highest specificity one of currently known vascular growth factors. VEGF is a highly specific vascular endothelial mitogen, which has a strong stimulating effect on the proliferation of endothelial cells through increasing vascular permeability, promoting the formation of tumor blood vessels. So it plays an important role on the tumor vascular endothelial cell proliferation and migration [29]. The VEGF family is a specific and potent proangiogenic factor, which consists of six groups including VEGF-A, -B, -C, -D, -E and the placental growth factor (PlGF). VEGF-A and VEGF-B are associated with angiogenesis [30,31]. It is by binding to its high affinity tyrosine kinase receptor (VEGFR) that VEGF achieves a variety of biological functions. Therefore, a remarkable approach to the treatment of cancer is to inhibit the VEGF/VEGFR signaling system [32]. Current research exhibiting, VEGFR family has five members. There are three main subtypes (VEGFR-1 (flt-1), VEGFR-2 (KDR/flk-1), VEGFR-3 (flt-4)) of VEGFR belonging to the tyrosine kinase receptor superfamily (RTKs), mainly distributed on the surface of vascular endothelial cells. They are mainly composed of three parts including the transmembrane region, the extracellular region with seven immunoglobulin-like domains, and the consensus tyrosine kinase sequence, which is interrupted by a kinase-insert domain [33,34]. The common features of these three receptors are that they all have tyrosine kinases insertion area in the catalytic domain, that tyrosine kinases activity is activated through ligand-receptor binding (LRB) and that receptor phosphorylation induces intracellular enzymes and other reactions [35–39]. All these features are very important in cell growth and differentiation. VEGFR-3 is largely restricted to lymphatic ECs, while VEGFR-1 and VEGFR-2 are expressed on the cell surface of most blood ECs (Endothelial Cells). The other two members of VEGFR family are nerve fibers factor −1 (neuroplin-1 NRP-1) and the nerve fibers factor −2 (neuroplin-2, NRP-2), which do not belong to RTKs and do not have the extracellular region with seven immunoglobulin-like or tyrosine kinase intracellular region. Therefore, they cannot become a separate receptor, only play a supporting role [40,41]. Various members of the VEGF family specificity bind to the above-mentioned receptors to function, VEGF-A mainly binding to VEGFR-1 and VEGFR-2, PlGF and VEGF−B binding to VEGFR-1, VEGF-C and VEGF-D binding to VEGFR-2 and VEGFR-3, VEGF-E only binding to VEGFR-2. The two non-tyrosine kinase receptor NRP-1 and NRP-2 bind with VEGF-B, PlGF and VEGF165 (VEGF-A subtypes) [42].

VEGFR-1, VEGFR-2 and VEGFR-3 play an important role in