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KDR/VEGFR-2 Receptor Tyrosine Kinase Inhibitors and 3D QSAR (CoMFA and CoMSIA) Study

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Review Article

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ABSTRACT

The review illustrates on the Vascular endothelial growth factor-A (VEGF-A) which shows pivotal roles in many angiogenic processes both in stable and pathological condition. Angiogenesis plays a key role in a number of pathology conditions with VEGFR-2 signals implicated in both tumour angiogenesis and diabetic retinopathy.

INTRODUCTION

The intricated, branched circulatory networks of vascular endothelial and supporting cells is essential for transporting oxygen, essential nutrients, and signaling molecules, removing of carbon dioxide and metabolic end products from cells, tissues, and organs. The process of development and growth of new capillary blood vessels from pre-existing vessels is called as Angiogenesis. It occurs in different physiological processes such as reproductive functions (ovular cycle, formation of the placenta), tissue repair (closing up of wounds and ulcers), inflammation [1-5] and ischemia [6-8]. Angiogenesis can however become pathological and contribute to the development of certain diseases like diabetic proliferative retinopathy [9], rheumatoidic polyarthritis [10,11], atherosclerosis, *development of numerous types of tumors* and the formation of metastases [12].

Vascular endothelial growth factor-A (VEGF-A) plays pivotal roles in many angiogenic processes both in normal and pathological conditions. VEGF-A [13,14] binds its tyrosine kinase receptor VEGFR-2 (Flk-1/KDR, Fetal liver kinase-1/Kinase insert Domain containing Receptor) with high affnity and regulates angiogenesis during the development of solid tumors [15-20]. Flk-1 is the murine homologue of human KDR, sharing 85% sequence homology and being 2 amino acids shorter.

VEGF LIGANDS AND RECEPTORS

Vascular endothelial growing factor (VEGF) represents a family of homodimeric glycoproteins which are most important for the embryonic development of the blood vascular system (vasculogenesis) [21], lymphatic system (lymphangiogenesis) [22-24] and in the new blood formation from pre-existing vessels (angiogenesis). In mammals, the VEGF family contains five members, VEGF-A, VEGF-B, VEGF-C, VEGF-D and placenta growth factor (PLGF).Members of the VEGF family reflects different affinities for one of the three VEGF tyrosine kinase receptors: VEGF receptor VEGFR-1, VEGFR-2 and VEGFR-3 [9].

VEGF-A binds to both VEGFR-1 and VEGFR-2, PLGF and VEGF-B bind exclusively to VEGFR-1.VEGF-C and VEGF-D pro-peptides are expressed initially as that bind the VEGFR-3. The mature, proteolytically processed VEGF-C and VEGF-D ligands can also bind to VEGFR-2.

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VEGFR-1 (Flt-1) expresses on haematopoietic stem cells [25-27], monocytes, macrophages [28-30] and vascular endothelial cells which is critical for haematopoietic cell development.VEGFR-2 (Flk-1/KDR) is shown on vascular endothelial cells and lymphatic endothelial cells and is critical for vascular endothelial cell development.VEGFR-3 (Flt4) expression is restricted to lymphatic endothelial cells and is critical for lymphatic endothelial cell development.

VEGF-A AND ITS RECEPTOR VEGFR-2

The human VEGF-A gene is located on chromosome 6p21.3. The coding area spans exactly 14 kb and contains eight exons. In mammals, VEGF-A exists in a number of different isoforms following alternative cutting of a single precursor mRNA. In humans, six VEGF-A splice variants have been detected: VEGF-$A_{189,}$ VEGF-A_{121}, VEGF-A_{165}, VEGF-A_{145}, VEGF-A_{183} and VEGF-A_{206}. VEGF-A_{165} is the most abundant and biologically active form and is expressed as a 46 kDa homodimer [31] formed of two 23 kDa subunits. VEGF-A is produced by a range of cells including smooth muscle vascular cells, macrophages and tumour cells.

VEGFR-2 is a type III transmembrane kinase receptor. The human VEGFR-2 gene, located on chromosomes 4q11–q12 encodes a full-length receptor of 1356 amino acids. It contains of an extracellular region formed of seven immunoglobulin [32-34] (Ig)-like domains, a short transmembrane domain, and a intracellular region consisting of single tyrosine kinase [35,36] domain, split by a 70 amino-acid insert. VEGFR-2 protein is initially translated as a 150 kDa protein inside the cell without significant glycosylation [37-39]. It is then processed by a chain of glycosylations to form a mature 230 kDa form that is expressed on the cell surface.

VEGF-A binds to the second and third extracellular Ig-like domains of VEGFR-2. Ligand binding induces receptor dimerisation and autophosphorylation. The binding of the dimeric VEGF ligand, to the Ig-like domains 2 and 3 of one receptor monomer [40,41], increases the probability of the second receptor monomer ties the already tethered ligand.

Once the two receptors are cross-linked to each other with simultaneous interaction via the ligand, their membrane-proximal Ig-like domains are held in close proximity so that low-affinity homotypic interactions among these domains further stabilises the receptor dimers. This allows for the exact positioning of the intracellular kinase domains resulting in autophosphorylation.

The major phosphorylation [42-44] sites are Y951 present in kinase-insert domain, Y1054 and Y1059 within the kinase domain, and Y1175 and Y1214 in the C-terminal tail of the receptor. Phosphorylation of specific tyrosine residues in the receptor creates a consensus sequence for the deployment of specific intracellular signalling proteins, via their Src homology 2 (SH2) domains. Phosphorylation [45-47] of Y951 creates a binding forming site for VEGF-receptor-association in protein (VRAP) also called T-cell-specific adapter molecule (TSAd). Phosphorylation of Y1175 creates a binding site for a number of signalling proteins such as PLC-γ , the adaptor protein Shb and the adaptor protein Sck. Phosphorylation of Y1214 creates a binding site for the adaptor protein Nck.

VEGFR-2 SIGNALLING IN TUMOUR ANGIOGENESIS AND THERAPEUTIC INHIBITION

Angiogenesis plays a role in a number of pathological conditions with VEGFR-2 signalling applied in both tumour angiogenesis and diabetic retinopathy [48-50]. Angiogenesis is very important for tumour formation as cancer cells have a relatively high metabolic demand for oxygen and nutrients to continous growth. How ever, the capillary and vascular network allows tumours to metastasise and spread to other sites in the body.

VEGF-A expression in cancer cells is induced during tumour formation by environmental stimuli such as hypoxia (low Oxygen tension) or by mutational genes of tumour suppressor genes (K-ras, p53 or HER2/ErbB2) or by activation of oncogenes [51,52]. Expression of VEGFR-2 is upregulated in the tumour vasculature compared with normal vasculature. Indeed, VEGFR-2 expression is a prognostic marker in the clinical outcome of patients with a variety of malignancies.

In 1971, Folkman first proposed the theory that stops angiogenesis which results in the arrest of tumour growth. This vision has now become a reality, with the arrival of a number of anti-angiogenic drugs in the clinic. These agents can be divided in two broader classes, some agents targeting the VEGF ligand and agents targeting the cell surface receptor.

Bevacizumab (Avastin®) [53-57] was afflicated the first anti-angiogenic drug to receive FDA approval for cancer treatment [58-60] and in february 2004, it was passed for use in combination with 5-fluorouracil-based chemotherapy for treatment of metastatic colorectal cancer [61-63]. Avastin is a humanised recombinant monoclonal IgG1 antibody which binds to and inhibits the biological activity of all VEGF-A isoforms.Now this drug is in clinical trails for use against a range of different cancers in combination with chemotherapy.

A number of pharmaceutical organisations and companies have developed small molecule inhibitors of the VEGFRs. These agents target RTKs and their ATP-binding sites, resulting in the blockade of downstream intracellular signalling pathways. Sunitinib [63-66] (Sutent®) is a two way targeting RTK inhibitor to VEGFR-2 and PDGFR-β, which exhibits anti-tumour activity.

Therefore, inhibition of the VEGFR-2 has evolved in an attractive strategy in the treatment of cancers.

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QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP (QSAR)

The number of compounds necessary for synthesis in order to study their bioactivities against a receptor experimentally using bioassays by placing 10 different substitution groups in 4 positions of benzene ring is 10^4.This takes huge amount of time as each compound has to be synthesized and tested for bioactivity [67-70] against receptor individually. The solution is to synthesize a small number of compounds and from their data deriving rules to predict the biological activity [71,72] of other analogous compounds. This enables the study of several substitutions on a common core in less time.

A QSAR is a mathematical bonding between biological activity of a molecular system and its geometric/chemical characteristics. QSAR attempts to find bonding between biological activity and molecular properties, so that these "rules" can be used to evaluate the activity of new compounds. These molecular properties/descriptors include parameters to account for hydrophobicity [73-76], topology [77-79], electronic properties [80,81], steric effects etc., which are determined empirically or by computational methods and activities used in QSAR model generation include measurements (IC_{50}, EC_{50}, ED_{50}, K_i, etc.) from biological assays.

QSAR's most general mathematical form is: Activity=f (physiochemical and/or structural properties).

3D-QSAR

Structure-activity relationships of traditional type for e.g., Hansch analysis usually do not take the 3D structures of the investigated compounds into account in an explicit manner. Instead, they use substituent parameters and indicator variables to describe the structural variations [82,83]. Extensions to the traditional QSAR approaches have been developed which explicitly uses geometry of the structures during the development of a QSAR model [84-87]. These new technologies are commonly referred as 3D-QSAR methodologies.

The presently most used 3D-QSAR techniques are:

CoMFA (Comparative Molecular Field Analysis) and CoMSIA (Comparative Molecular Similarity Indices Analysis).

CoMFA

CoMFA is based on the assumption that changes in biological activity correlate with changes in the steric and electrostatic fields of molecules. It calculates steric fields using Lennard-Jones potential and electrostatic fields using a Coulombic potential.

The following steps have to be considered to develop a CoMFA model:

1. Selection of training set compounds
2. Identification of active conformations
3. Molecular alignment
4. Calculation of field values
5. Partial Least Square (PLS) analysis
6. Validation using test set compounds
7. Interpretation of results (contour maps)
8. Predictions of new compounds

CoMSIA

CoMSIA is an extension of the CoMFA methodology. In CoMSIA, five different similarity fields (electrostatic, hydrophobic [88-91], Steric, H-bond donor [92-96], and H-bond acceptor [97-100]) are correlated with biological activity. These fields were selected to cover major contributions to ligand binding.

In general, CoMSIA similarity indices $A_{F,k}$ between the compounds of interest is computed by placing a probe atom at the intersections of the lattice points using the following formula:

$$A^q_{F,k}(j) = -\Sigma_{i=1..n} W_{probe,k} W_{ik} \exp(-\alpha r_{iq}^2)$$

Where A is the similarity index at grid point q, summed over all atoms, i, of the fragment j under investigation.

$W_{probe;k}$ is the invetigated atom with a radius of 1 A˚, charge +1, hydrophobicity +1, hydrogen bond donating +1, hydrogen bond accepting +1.

W_{ik} is the actual value of physicochemical k property of atom i.

r_{iq} is the corelative distance between tne probe atom at grid poinr q and atom i of test molecule.

α is the attenuation factor with default value of 0.3.

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