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Review Article

Neuropilins - Past, Present and Future: A Review of Its Anti-Neoplastic Potential

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Abstract: Recently, cancer progression has been linked to a trans-membrane receptor, neuropilin. Studies show that neuropilins are widely distributed in the body and these receptors appear to control the vasculirization of tumors. Neuropilins 1 and 2 are known to be involved in angiogenesis and vascular development and are receptors for vascular endothelial growth factor (VEGF) and the class 3 semaphorins. Angiogenesis, which is a feature of many malignancies, is aided by increased neuropilin expression. Hence, high neuropilin expression correlates with tumor progression and poor prognosis. Attempts are being made to suppress tumor growth and invasion by employing agents that suppress angiogenesis. This is of great interest, because blockade or inhibition of these molecules may be used as therapeutic agents in cancer therapy. In this review, the molecular biology and current knowledge of neuropilins are explored with a view to identifying their therapeutic potentials. In conclusion, neuropilin targeted intervention may be relevant as anti-cancer therapy.

Keywords: Neuropilin, Semaphorins, Angiogenesis, VEGF, Malignancy, Receptor, Therapy

1. Introduction

Neuropilins (NP) are groups of protein receptors for class three semaphorins and members of the vascular endothelial growth factor (VEGF) family, with essential roles in neuronal patterning and cardiovascular development respectively [1-4]. These proteins are non-signalling trans-membrane bound co-receptors to a tyrosine kinase receptor for both VEGF and semaphorins. They have the ability to bind with these two biologically unrelated molecules viz-class three semaphorins and VEGF family [6, 7]. These neuropilins are of two forms – Neuropilins 1 (NP1) and Neuropilins 2 (NP2). Both are transmembrane glycoproteins and co-receptors for a class of proteins called semaphorins [7, 8]. Neuropilins are receptors or co-receptors for multiple ligands, including class three semaphorins, VEGF, heparin-binding proteins, fibroblast-growth factor, and placental growth factor [7, 8]. These properties have been explored in medical therapeutics. This article reviews the biological features of neuropilins with a view to assessing its anti-cancer benefits.

1.1. Historical Background

Neuropilins have been known as membrane receptors and were originally discovered in the nervous system of a developing *xenopus* (tadpole) [8, 9]. They were first identified by Takagari and his research teammates in 1987. They identified NP1. A decade later, Chen et al isolated NP2 by polymerase chain reaction [8, 10, 11, 12].

1.2. Body Distribution / Molecular Strucure

Neuropilins are present in all vertebrate animals, including man [7]. Human neuropilins 1 and 2 (NP1 & NP2) genes are located on chromosome 10q12 and 2q34 respectively, and both encode full-length proteins [13, 14]. The molecular masses of NP1 and NP2 are between 130-140 kDa (NP1 has 923 amino acids, while NP2 has 926 amino acids). Both have 17 exons and span over 120kilobytes and greater than 112 kilobytes for NP1 and NP2 respectively. In addition, NP1 are found primarily in arterial endothelium and is a receptor for semaphorins 3A, 3C, 3F while NP2 is highly expressed and

localized in venous and lymphatic endothelium and binds to BB, 3C, 3D and 3F of the class three semaphorins [15-18]. The semaphorins are members of a family of axons or guidance molecules that signal by interaction with transmembrane receptor complexes that incorporate neuropilins, as co-receptors to plexins which are major receptors for all semaphorin family members [19-21]. NP1 interacts with VEGF A, B, E and platelet growth factor (PGF) whereas NP2 interact with VEGF A, B, C, and D [19, 22]. Generally, Neuropilins contain the following four domains:

-Complement c1r/c1s, Uegf, BMP1 (CUB).

-Coagulation factor 5/8 type, C-terminal (discoidin domain)

-MAM domain (for meprin, A-5 Protein, and receptor protein tyrosinephosphatase mu)

-C-terminal neuropilin [7, 23, 24].

2. Review of Neuropilin Functions and Its Antineoplastic Potentials

2.1. Biologic Functions

Neuropilins are high affinity receptors for semaphorin 3 family [8, 19, 25, 26, 27, 28]. Only class three semaphorins out of the existing eight classes bind to neuropilins (i.e. semaphorins 3A, 3B, 3F). Neuropilins function together with plexin family signaling receptors to control sema-3 mediated axon guidance which is critical for patterning of the nervous system [29, 30]. Based on this, neuropilins function as central receptors to integrate competitive VEGF and semaphorin signals. neuropilins transduce signals for the three VEGFR family members [19, 21, 31]. They function in multiple steps of angiogenic cascade including binding of VEGF ligand regulating cellular activation by VEGFR and controlling directional migration [21, 32]. Neuropilins directly couple with integrins to control cellular function and adhesions. Pathologically, integrins are associated with cancer invasion, increased fibronectin assembly, stem cell fate determination, breast cancer initiation, and adhesion to laminin [33]. Neutropilins function as versatile co-receptors that can bind to a number of growth factors and couple with cognate receptor tyrosine kinase (RTK) signaling pathways including fibroblasts growth factor (FGF); platelet-derived growth factor (PDGF) and transforming growth factor (TGF-β) [21].

2.2. Neuropilin Expression in Normal Cells

The expression of neuropilins in various body cells is a common finding. For example, NP1 has also been found to be fully expressed in non-vascular cell types [34]. NP1 has also been found in the developing nervous system of *xenopus* tadpoles [30, 35]. In humans, NP have been fully expressed in body cells such as osteoblasts, dendritic cells, neuro-endocrine cells of the gastrointestinal tract, T-cells of the bone marrow, fibroblasts and adipocytes, renal and glomerular mesangialcells [1]. Again, neuropilins are said to be widely expressed in normal matured and developing vascular smooth muscles, endothelial cells and human vascular endothelium [36].

2.3. Neuropilin Expression in Tumor Cells-Implication in Cancer

Both NP1 and NP2 are fully expressed in several cell types of tumors [37]. Expression of one or both have been linked with tumour progression and/or poor prognosis. In man, the expression of NP has been linked to tumor growth and invasion of cancer of prostrate colorectal cancer, lung cancer, breast cancer and astrocytoma. Expressions of NP1 and NP2 have been implicated in the progress of certain cancers [36, 38]. The table 1 below gives a summary of this:

Table 1. *Showing Neuropilin Expression in Certain Malignancies.*

Neuropilin expression	Tumor type	Effects on tumor
↑ NP1	Prostate Cancer	Increased tumor progression Poor prognosis [39]
↑ NP1	Colorectal cancer	↑ Tumor Growth ↑ Tumor invasion [40]
↑ NP1	Lung Cancer	Increased invasion of malignancy [41]
↑ NP1	Breast cancer	Increased invasion of malignancy [42]
↑ NP1	Astrocytoma	Invasion increased [43]
↑ NP1	Bladder cancer	Advancing tumor stage/grade [44]
↑ NP2	Non-small cell	Worsening prognosis of lung cancer [41]
↑ NP1	Lung cancer	
↑ NP2	GIT carcinoid tumor	Tumor progression [45]
↑ NP1	Squamous cell cancer	Cell migration and invasion [46]
↑ NP1	Oral squamous cell cancer (OSCC)	Lymphoid nodal metastatis Poor prognosis [47]
↑ NP1	Pancreatic cancer	Decrease in tumor growth [48]
↑ NP	Melanoma	Increased tumor aggression [49]

↑- signifies increase in levels.

2.4. Prospective Uses/Applications of Neuropilins

A. CANCER THERAPY

NP1 is a therapeutic target protein in the treatment of leukemia and lymphoma. NP1 has been known to play a major role in tumor angiogenesis, axon guidance, cell

survival, migration and invasion [50]. There is an increased expression of NP1 in leukemia and lymphoma cell lines. Inhibition of NP1 is found to inhibit tumor cell migration and adhesion [38, 51]. Based on this, NP1 is a target for cancer therapies. Since Folkman *et al* hypothesized that inhibition of angiogenesis in solid tumors could be used to treat cancer, many potential inhibitors have been tested, while some are on the way to being approved [52] in this regard, NP1 is seen as an emerging target. This is so vital because it is a co-receptor of VEGFblocking blood supply to the tumors. A synthetic peptide of neuropilins EG3287 was made in 2005 and is able to block VEGF. This induces apoptosis in tumor cells, with decreased NP expression. In vivo studies show that NP1 inhibits the progression of acute myeloid leukemia (AML) in mice. Antagonism of NP1 has been shown to inhibit tumor cells migration and adhesion [41, 53].

Paradoxically, soluble NP1 has a reversible effect on membrane bound NP1 i.e. anti-VEGF activity. This inhibits progression of acute myeloid leukemia in mice in vivo studies [54].

B. CANCER DIAGNOSIS

C. PROGNOSIS OF CANCER

D. ASSESSMENT OF TUMOUR METASTASIS

Measuring levels of $VEGFR_{165}$ /NP1/NP2 in biological specimens obtained from patients (blood, tissue, semen, stool, urine, sputum, CSF, supernatant from cell lysate) and comparing levels to a baseline for that type of specimen can be used for diagnosing, prognosis, and assessing tumor metastasis in cancers especially cancer of the prostrate, haemangioendothelioma and breast cancer. A level of $VEGFR_{165}$/NP1/NP2 greater than baseline levels is indicative of cancer. Expression of $VEGFR_{165}$ /NP1/NP2 in a tumor sample greater than the baseline level for that particular tissue indicates a higher risk of tumor metastasis. Levels of $VEGR_{165}$/NP1/NP2 are measured by assessing the protein directly or indirectly by measuring the transcript (MRNA) encoding the VEGFR 165/NP1/NP2 using RNA depending polymerase chain reaction (PCR) e.g. reverse transcriptase PCR and northern blot analysis [54].

E. THERAPEUTIC ANGIOGENESIS

Ischemic vascular diseases are currently being resolved with a view to using VEGFs to stimulate angiogenesis, arteriogenesis and lymphangiogenesis. VEGFs are delivered as recombinant protein or via gene transfer for the treatment of myocardial infarction or peripheral ischaemia [55, 56].

F. TREATMENT OF CHOROIDAL AND RETINAL NEOVASCULARIZATION

Inhibiting VEGF is the gold standard treatment for vascular age-related macular degeneration. This is important in preventing retinal edema and neo-vascularization in diabetic retinopathy [57].

3. Conclusion

Neuropilins are expressed in various body cells and in many forms of cancer. In many cases, their expressions in cancers are linked with increased tumor invasion, progression and worsening prognosis. Neuropilins are class 3 semaphorin receptors. Angiogenesis, which is a physiological process of new blood vessel formation, is an important component of tumor invasion and progression. Targeting neuropilin is an indirect way of suppressing tumor potential. Hence, neuropilin blockade is seen in this regard as a promising therapeutic intervention.

Conflict of Interest

The authors declare that none exists.

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