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Review Article

N-Methyl-D-Aspartate (NMDA) Receptors: Therapeutic Target against Cancer

Abstract

Glutamate (Glu) mainly acts as an excitatory neurotransmitter in the central nervous system controlling variety of neuro-physiological functions like synaptic signaling, learning, memory, etc. However, uncontrolled or excessive production of glutamate is neurotoxic and can damage neurons by over activation of glutamate receptors termed as "glutamate excitotoxicity". Apart from excitatory neurotransmitter role of glutamate, some recent observations suggest glutamate as a potential growth factor for tumor development. Till date suitable therapy for cancer is lagging behind due to several side effects. In the present review article, a link between ionotropic glutamate receptor i.e. N-methyl-D-aspartate (NMDA) receptors (NMDARs) and cancer has been mainly focused. Regulation of cancer cells by NMDARs is an emerging or evolving concept. Besides neurons, NMDAR subunits are expressed in various types of cancer cells. Based upon existing literature, we suggest that NMDARs could serve as a therapeutic target against various types of cancer.

Introduction

In the mammalian central nervous system (CNS), glutamate, a nonessential amino acid, plays an important role as neurotransmitters and is responsible for fast excitatory synaptic signaling in the brain. Glutamate controls several physiological processes like learning, memory and behavior; however excess concentration of glutamate is detrimental for neurons that can lead to neuronal cell death known as excitotoxicity [1]. Higher levels of glutamate are implicated in the pathophysiology of various neurodegenerative disorders like epilepsy, hypoxia or stroke [2].

Beside its role as neurotransmitter, glutamate also regulates proliferation, migration and survival of neuronal progenitor cells as well as immature neurons during brain development [3,4]. Uncontrolled propagation and migration are characteristic features of neoplastic cells; thereby suggesting glutamate as a potential growth factor for tumor development [1]. This hypothesis was validated by studies that showed neurotoxic quantities of glutamate by glial tumor cells *ex vivo* (in surgical specimens) [5] as well as *in vitro* in glioma cell lines, where extracellular glutamate concentrations up to 500 μmol/L were demonstrated [6]. Further xenograft studies proved that experimental tumors generated from cells that release high amounts of glutamate grow more aggressively compared with non-modified cells which release moderate amount of glutamate or from non-secreting cells [5]. Later studies have also shown that excessive concentration of glutamate (100 μM) in the extracellular space at the tumor margin in glioblastoma bearing patients [7] leads to neuronal cell death, which in turn promote tumor growth [8] and possibly relates to epileptic seizures in glioma patients [9]. This observation was supported by a study that proved the relationship between increased levels of excitatory neuropeptide, dynorphin 1-17 that comprises glutamate and cell death or surgery related tissue injury *in vivo* in epilepsy patients [10].

In the recent past it has been observed that cells from non-CNS cancers secrete glutamate, e.g., MDA-MB-231 (human breast), B16F1 (mouse melanoma) and MATLyLu (rat prostate) cancer cell lines release significant amount of glutamate into their extracellular environment [11]. A recent study has reported that prostate cancer bearing patients have serum glutamate levels directly correlating with Gleason score (≤6 vs. ≥8) and primary prostate cancer aggressiveness [12]. Increased levels of glutamate in chronic pancreatitis (CP) and pancreatic ductal adenocarcinoma (PDAC) tissues suggested that glutamate might serve as a molecular switch that decreases the threshold of k-ras-induced oncogenic signaling and enhances the chance of malignant transformation of pancreatic cancer precursor lesions [13]. Glutamate and synthetic GluR agonists stimulated proliferation of A549 lung cancer cells *in vitro* [14-16] and invasion of PDAC [13]. Above described evidences thus suggests that glutamate can act as a growth factor and signal mediator in non-neuronal tumor tissues.

Various functions of Glu are mediated by appropriate glutamate receptors. Structure and function of glutamate receptors were reviewed in detail by Lau and Tymianski [17]. Glutamate receptors are mainly of two types: metabotropic glutamate receptors (mGluRs) - which belong to the superfamily of G-protein coupled receptors and ionotropic glutamate receptors (iGluRs) – which form ion channels. N-methyl-D-aspartate (NMDA) receptors (NMDARs) are iGluRs and present review is mainly focused on NMDARs.

NMDARs are assembled by combination of seven subunits: NR1, NR2A/B/C/D, NR3A/B, each of these subunits being product of separate gene. NMDARs mainly consists of two obligatory NR1 subunits and two out of the four types of regulatory subunits NR2A, B, C or D, which assemble as a dimer of dimers and the resulting complex so formed can also combine with either NR3A or NR3B by replacing one of the NR2 subunits [1]. Glycine is required as

natural agonist for NMDARs [18,19]. NR1 subunit is essential for calcium conductivity of the channel whereas NR2 and NR3 subunits determine electrophysiological and pharmacological properties of the receptor [20].

NMDAR regulates mTOR signaling

Activation of NMDAR affects signaling activity by mammalian target of rapamycin (mTOR), a serine/threonine kinase, contained within the mTORC1 complex, which influences transcription and translation [21]. NMDAR activation leads to Ca^{2+} dependent activation of calcineurin, a protein phosphatase, whose substrate is Striatal enriched protein tyrosine phosphatase (STEP). STEP then acts on phosphorylated ERK1/2, an extracellular signal-regulated kinase that drives mTOR signaling [22,23]. Therefore, NMDA receptor activation limits the duration of signaling by ERK1/2, which diminishes mTOR signaling activity. Dysregulated mTOR signaling activity is mainly implicated in pathogenesis of malignancy and metastasis and serves as a chemotherapeutic target [21]. Thus, mTOR signaling serves as a connecting link between NMDAR and cancer; NMDAR modulates mTOR signaling pathway that in turn can regulate cancer cell proliferation and progression. Moreover, it can be concluded from above facts and figures that NMDAR could be used as a therapeutic target against cancer cells. Similarly, it was suggested by Li and Hanahan (2013) that NMDAR signaling pathway offers a potentially important target for future cancer therapeutics [24].

Expression of NMDARs in cancer cells

Earlier glutamate signaling was thought to be restricted to CNS; later on studies confirmed the existence of glutamate receptors in peripheral organs and neoplastic or cancerous cells [25,26]. Primary studies during mid-nineties provided evidence that labeled NMDA agonist [3H]-MK801 couples with tumor cells of CNS and *in vitro* glutamate application resulted in Ca^{2+} influx into these tumor cells [27]. Experimental studies have also confirmed the involvement of NR1 and NR2C subunits in samples from CNS tumor [28,29; Table 1]. NR1 subunit of NMDAR is present in CNS neoplasms whereas, it is absent in glioma cell lines, thereby suggesting non-functional NMDARs in the glioma cells [30].

As summarized in Table 1, majority of NMDARs expression is reported in peripheral cancers. NR1 subunit of NMDAR is highly expressed in prostate cancer samples, in contrast its expression was very low or absent in normal prostate tissue and benign prostate hyperplasia [1]. Similar expression pattern of NMDAR was found in normal colon and cancerous colon [31]. Immunohistochemical expression of NR1 subunit was found in majority of small-cell lung [32] or breast cancer samples, where NR2B subunit was also detected [33]. NR2B subunit is also implicated in enhancing tumor invasion and aggressiveness in pancreatic neuroendocrine tumorigenesis (PNET) model [24]. Different combinations or single subunits of NMDARs were demonstrated in cell lines derived from colon cancer [30,34], breast cancer [30,33], oral cancer [35], laryngeal carcinoma [36], lung cancers [15,16,32], prostate cancer [31], thyroid cancer [30] as well as in gastric [37,38], esophageal [39], and hepatocellular carcinomas [34].

NR2D subunit is mainly expressed prenatally in rapidly dividing CNS cells while it declines postnatally [1]. In adults, NR2D subunit is restricted to selected brain regions [40,41]. Therefore, expression of NR2D subunit in all the virtually analyzed cancer cell lines suggested that re-expression of NR2D subunit could be correlated with their proliferative potential.

Modulation of NMDAR (activation and antagonism) in cancer cells

Modulation of expression of NMDAR subunits affects behavior of cancer cells; silencing NR2A subunit gene inhibited proliferation of gastric cancer cells and cell cycle progression that leads to increased proportion of cells in G1 phase [38]. Knocking down NR1 gene reduced cell viability of lung cancer cells TE671 and A549 [42], (Table 2). Inhibition of NMDAR by MK801 (non-competitive NMDAR antagonist) has also shown antitumor effects while treating various xenograft tumors [32,33].

Two non-competitive NMDAR antagonists, MK-801 (dizocilpine) and memantine have shown to possess concentration dependent cytotoxic effects on human lung adenocarcinoma cells (A549) grown *in vitro*. These cells express NR1 and NR2B subunits of NMDAR. In A549 cell line, MK-801 declined immunoreactive levels of phosphorylated ERK1/2 in a concentration dependent manner

Table 1: Summarized view of NMDAR subunits expression in various cancer cell types.

Cancer type	NMDAR subunit expressed	References
Brain tumor	NR1 and NR2C subunits	[28,29]
Prostate cancer	NR1 subunit	[1,31]
Colon cancer	NR1 and NR2B subunits	[30,31,34]
Lung cancer	NR1 and NR2B subunits	[15,16,32]
Breast cancer	NR1 and NR2B subunits	[33,34]
Pancreatic tumor	NR2B subunit	[24]
Oral cancer	NR1 subunit	[35]
Laryngeal cancer	NR1, NR2A, NR2B, NR2C, NR2D and NR3A subunits	[36]
Thyroid cancer	NR1 subunit	[30]
Gastric cancer	NR1, NR2A, NR2B, NR2C, NR2D, NR3A and NR3B subunits	[37,38]
Esophageal cancer	NR2B subunit	[39]
Liver cancer (Hepatocellular carcinoma)	NR1, NR2A, NR2B, NR2C, NR2D, NR3A and NR3B subunits	[34]

without altering total ERK1/2, further it was found that culturing A549 with MK-801 decreased activation (i.e. phosphorylation) of the cAMP-response element binding protein (CREB), which is involved in regulating transcription of various genes involved in cell cycle like p21 (tumor suppressor protein). MK-801 up-regulates p21 expression in A549 cells [21]. NMDAR is also implicated in regulating proliferation of breast cancer cells, as MK-801 and memantine diminishes proliferation and declined viability of breast cancer cell lines *viz.* MCF-7 and SKBR3 [21], (Table 2). In patients receiving whole brain radiotherapy, memantine prevents cognitive dysfunctions [43]. Memantine was also found to prevent post-mastectomy neuropathic pain as well as cognitive dysfunctions that could ultimately lead to improved life quality in cancer patients [44], (Table 2).

Thus, it can be inferred from above described experimental evidences that NMDARs plays critical role in proliferation and progression of cancer cells, as inhibition of NMDAR diminishes growth of cancerous cells (Figure 1). Li and Hanahan (2013) also suggested that NMDAR antagonists can be used for treating certain human cancers [24].

In contrast, NMDAR activation was found to suppress the outgrowth of keratinocytes in epithelialization process, which may be suitable to suppress tumor invasiveness [45-47], (Table 3). NR2B subunit of NMDAR is now emerging as a tumor suppressor gene; hypermethylation of its promoter region and silencing of its expression was seen in 12 out of 12 esophageal squamous cell carcinoma (ESCC) cell lines and in 55 of 61 (~90%) specimens of primary ESCC. Expression of NR2B subunit at mRNA level was almost absent or found to be declined in six gastric cancer cell lines (MKN1, MKN7, NKN74, AZ521, NUGC4 and NUGC3), as compared to normal stomach where vigorous expression was found [21], (Table 3).

Table 2: Effect of NMDAR inhibition in various types of cancerous cells.

Cancer cell type	Effect of NMDAR inhibition	References
Gastric cancer cells	Inhibition of NR2A subunit suppresses the growth of cancerous cell as well as cell cycle progression	[38]
Lung cancer cells	a) Silencing NR1 gene declined viability of cancerous cells b) Non-competitive NMDAR antagonists; MK-801 (dizocilpine) and memantine showed cytotoxic effects on A549 cells (lung cancer cells) grown in vitro.	[42] [21]
Breast cancer cells	MK-801 and memantine inhibited proliferation and declined viability of breast cancer cell lines MCF-7 and SKBR3.	[21]
Brain cells	a) Memantine prevents cognitive disturbances caused during brain radiotherapy b) Memantine also prevented post-mastectomy neuropathic pain as well as cognitive dysfunction and enhanced quality of life in cancer patients	[43] [44]

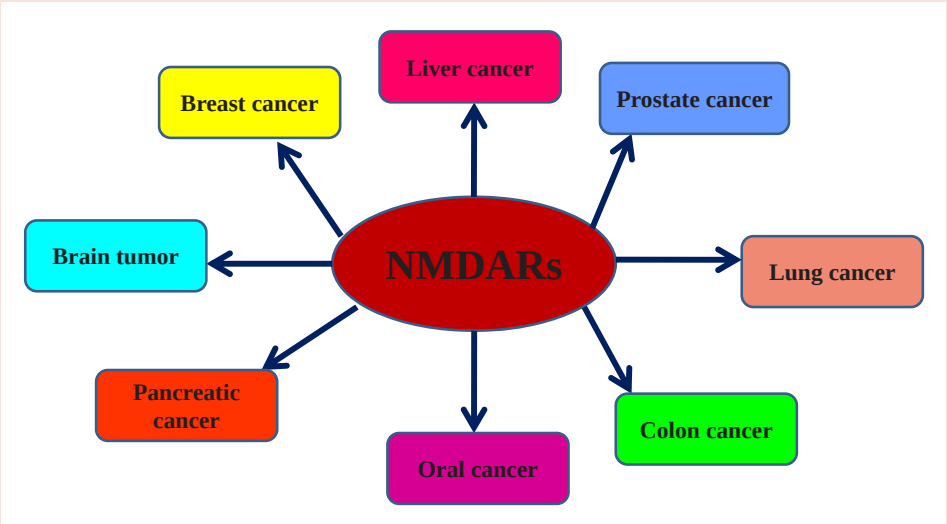

Figure 1: Implication of NMDARs in pathophysiology of various types of cancer.

Table 3: Effect of NMDAR activation in various types of cancerous cells.

Cancer cell type	Effect of NMDAR activation	References
Keratinocytes	NMDAR activation suppresses the outgrowth of keratinocytes during epithelialization process and thereby, inhibits tumor invasiveness	[45-47]
Esophageal cancer	NR2B subunit behaves as a tumor suppressor gene and hypermethylation of NR2B silences its expression in these cancer cell lines	[21]

Concluding Remark

NMDARs are mainly present in neurons and implicated in various neurological disorders via glutamate mediated excitotoxicity. Recent observations suggest the presence of functional NMDAR and expression of NMDAR subunits in various types of cancer cells (Figure 1). mTOR signaling pathway plays crucial role in pathogenesis of tumor cells and this signaling pathway has been recently reported to be regulated by NMDARs. Thereby, suggesting NMDAR might be involved in regulating growth of cancer cells via mTOR signaling pathway. Various experimental studies have concluded that activation of NMDARs is implicated in growth of cancer cell and inhibition of NMDARs declines the cancerous growth. At the same time, some reports have reported the anti-proliferative and tumor suppressive potential of these NMDARs. This may be due to the diverse role of NMDARs in different types of cancer cells. Thus, whether NMDAR activation or NMDAR antagonism will act as an anti-cancer agent varies in different types of cancer cells (e.g. lung, breast, prostate, etc). Expression of different NMDAR subunits in various types of cancer models will provide more precise information about involvement of particular subunit of NMDAR in specific cancer type, so that only selective subunit can be targeted for treating particular type of cancer. Altogether, NMDARs could serve as better and safer alternative for cancer therapy.

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