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Invited review

Metabotropic glutamate receptors in cancer

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ABSTRACT

Metabotropic glutamate receptors (mGluRs) are widely known for their roles in synaptic signaling. However, accumulating evidence suggests roles of mGluRs in human malignancies in addition to synaptic transmission. Somatic cell homeostasis presents intriguing possibilities of mGluRs and glutamate signaling as novel targets for human cancers. More recently, aberrant glutamate signaling has been shown to participate in the transformation and maintenance of various cancer types, including glioma, melanoma skin cancer, breast cancer, and prostate cancer, indicating that genes encoding mGluRs, GRMs, can function as oncogenes. Here, we provide a review on the interactions of mGluRs and their ligand, glutamate, in processes that promote the growth of tumors of neuronal and non-neuronal origins. Further, we discuss the evolution of riluzole, a glutamate release inhibitor approved for amyotrophic lateral sclerosis (ALS), but now fashioned as an mGluR1 inhibitor for melanoma therapy and as a radiosensitizer for tumors that have metastasized to the brain. With the success of riluzole, it is not far-fetched to believe that other drugs that may act directly or indirectly on other mGluRs can be beneficial for multiple applications.

This article is part of the Special Issue entitled 'Metabotropic Glutamate Receptors, 5 years on'.

Contents

1. Glutamine and glutamate

Glutamate plays an innate role in the human central nervous system as an excitatory neurotransmitter in processes such as learning and memory formation (Alix and Domingues, 2011; Fairman and Amara, 1999). Its role in cellular homeostasis is related to both its function in nitrogen metabolism and disposal, as well as its use as a metabolic fuel for energy-producing pathways (Dimski et al., 2008; Kelly and Stanley, 2001; Spanaki and Plaitakis, 2012). In addition, it has long been established that excess glutamate causes neuronal excitotoxicity; more recent findings have also implicated glutamate signaling in transformation and progression

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of various cancers (Prickett and Samuels, 2012; Ribeiro et al., 2010; Willard and Koochekpour, 2013). Glutamine is preferred as a fuel in tumor cells over glucose because of its properties enabling it to act to fulfill energy requirements as well as serve as an intermediate for macromolecule synthesis (Deberardinis et al., 2008; Moreadith and Lehninger, 1984; Wall et al., 2013). The dual role of glutamine derives from its structure. Reactions such as nucleotide synthesis may directly use its γ-nitrogen, whereas the α-nitrogen and its carbon skeleton can be used indirectly in reactions for energy production and biosynthesis (Gaglio et al., 2009). Cell growth requires these metabolic intermediates, and is propagated by the conversion of glutamine to glutamate by phosphate-dependent glutaminase (GLS) in the inner mitochondrial membrane (Fig. 1) (Cairns et al., 2011; Marie and Shinjo, 2011). This enzyme is overexpressed in many tumor types, and is a primary driver of glutamine consumption in cancer cells, leading to large intracellular pools of glutamate and subsequent glutamate release, the implications of which will be discussed later in this chapter (Cairns et al., 2011; Marie and Shinjo, 2011; Wall et al., 2013).

The conversion of glutamine to glutamate and ammonia constitutes the first and rate-limiting step of glutaminolysis. The resulting glutamate is used as a primary source of energy for proliferating cells, but can then be further metabolized to α-ketoglutarate in the mitochondrial matrix. Subsequent breakdown generates NADPH for use as an electron donor, which is also used to maintain glutathione (GSH), a key antioxidant, in its reduced state, thus keeping oxidative stress in check in rapidly growing cells (DeBerardinis et al., 2007; Estrela et al., 2006; Wall et al., 2013). Recently, several groups identified reductively metabolized glutamine as the major carbon source during hypoxia and limited respiration. Reductive metabolism is known to be preferred within the hypoxic conditions of most tumor environments, the result of a tumor's outpacing the development of an effective blood supply, among other conditions, and is due to the stabilization of a transcription factor, hypoxia-induced factor 1α (HIF-1α). Notably, HIF-1α induction and reductive metabolism occur in tumor cells growing in normoxic conditions as well, pointing to a more general role in sustaining tumor growth (Fendt et al., 2013; Filipp et al., 2012; Gameiro et al., 2013; Gao et al., 2009; Karakas et al., 2015; Niklas and Heinzle, 2012; Sun and Denko, 2014; Wise et al., 2008, 2011; Zamboni, 2011) (see Table 1).

2. mGluRs in cancer

Overexpression or aberrant expression of GPCRs has been detected in many cancer cell types, and contributes to tumor cell growth by paracrine or autocrine signaling, maintaining an activated state that leads to enhanced cellular proliferation via downstream effector proteins (Table 2) (Bhowmick et al., 2004; Burger et al., 1999; Cheng et al., 2008; Takayama et al., 1997). In particular, mGluRs have been shown empirically to be the predominant mediators of glutamatergic signaling in many cancers (Khan et al., 2011; Koochekpour, 2013; Martino et al., 2013; Speyer et al., 2014; Teh and Chen, 2012; Zhang et al., 2015). The mechanisms by which mGluRs modulate peripheral cell transformation and tumor growth are postulated to be either ectopic expression of wild type mGluRs, increased proliferative signals arising from receptor overexpression, mutations, or expression of polymorphic

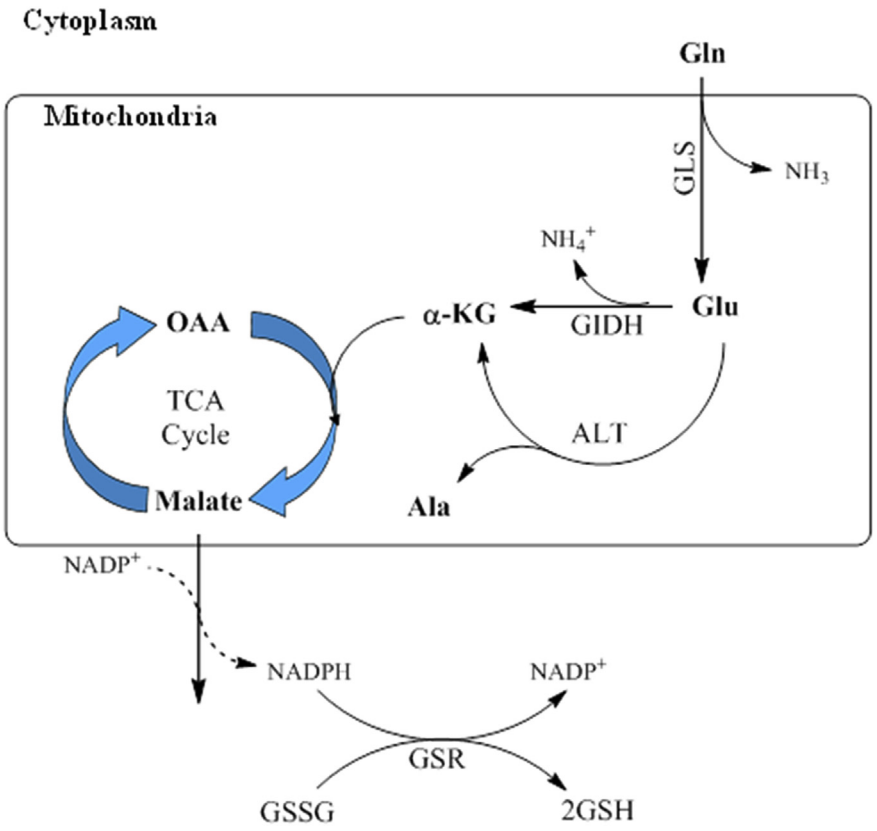

Fig. 1. Glutamate metabolism in the mitochondria. Glutamine (Gln) is converted to glutamate (Glu) by the enzyme glutaminase (GLS) releasing both Glu and ammonia into the cytosolic compartment of the inner mitochondrial membrane. Glu is then metabolized to α-ketoglutarate (α-KG) either by oxidative deamination by glutamate dehydrogenase (GIDH) or alanine transaminase (ALT). α-KG is metabolized in the tricarboxylic acid (TCA) cycle to oxaloacetate through the production of malate. Malate oxidation to pyruvate in the cytosol generates NADPH which is used to maintain glutathione in its reduced state.