Seminars in Cell & Developmental Biology 43 (2015) 22–32

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Amino acid management in cancer

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ARTICLE INFO

Article history:
Received 16 June 2015
Received in revised form 21 July 2015
Accepted 9 August 2015
Available online 12 August 2015

Keywords:
Amino acids
Metabolism
Cancer
Serine
Glutamine
mTOR

ABSTRACT

Amino acids have a dual role in cellular metabolism, as they are both the building blocks for protein synthesis and intermediate metabolites which fuel other biosynthetic reactions. Recent work has demonstrated that deregulation of both arms of amino acid management are common alterations seen in cancer. Among the most highly consumed nutrients by cancer cells are the amino acids glutamine and serine, and the biosynthetic pathways that metabolize them are required in various cancer subtypes and the object of current efforts to target cancer metabolism. Also altered in cancer are components of the machinery which sense amino acid sufficiency, nucleated by the mechanistic target of rapamycin (mTOR), a key regulator of cell growth via modulation of key processes including protein synthesis and autophagy. The precise ways in which altered amino acid management supports cellular transformation remain mostly elusive, and a fuller mechanistic understanding of these processes will be important for efforts to exploit such alterations for cancer therapy.

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1. Introduction

Proliferative cells alter their metabolism to support the biosynthetic reactions required for accumulation of biomass; indeed, alterations in tumor cell metabolism are recognized as a hallmark of cancer [1–3]. Robust macromolecular biosynthesis is required to support a proliferative cell metabolism [4], and proper sensing of the diverse nutrients required to support such biosynthesis is important to orchestrate these complex events [5]. Proliferative metabolism is supported by cellular programs which ensure that there is sufficient nutrient uptake and energy generation, management of redox potential, appropriate activation of autophagy to recycle macromolecules and damaged organelles, and elimination of toxic byproducts [1]. As such, alterations in these processes have been described over the past decades with increasing levels of sophistication, and strategies which target the altered metabolism of cancer are emerging [6].

In particular, it is becoming more apparent that proper amino acid management is critical to support proliferative metabolism via alterations in pathways that support their biosynthesis and

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http://dx.doi.org/10.1016/j.semcdb.2015.08.002
1084-9521/

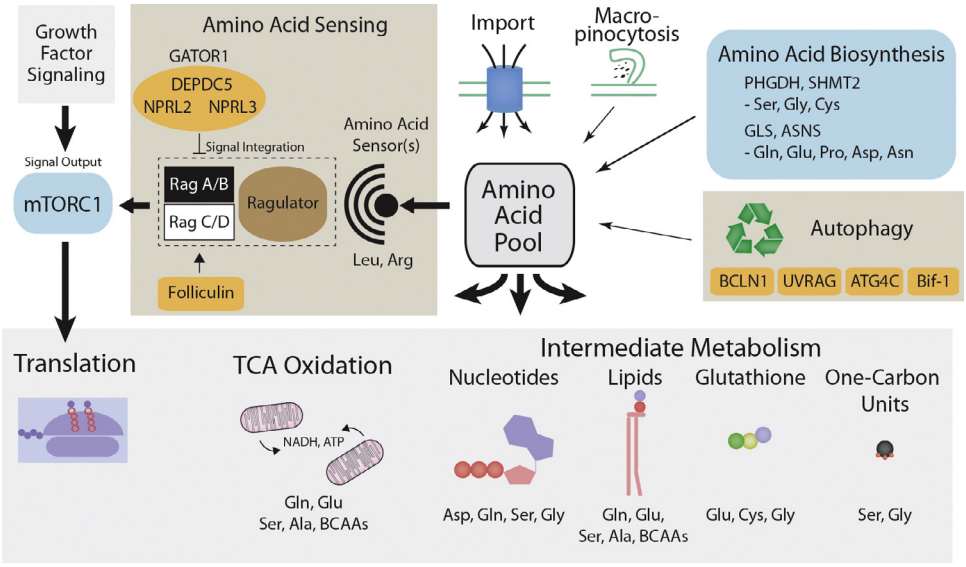

Fig. 1. Amino acid sensing and biosynthesis are altered in cancer. Amino acid import and biosynthesis, as well as the processes of autophagy and macropinocytosis contribute to the pool of amino acids available to the cell for macromolecular biosynthesis. Amino acid biosynthetic pathways are activated in subsets of cancer and drive the production of specific amino acids and their utilization as intermediate metabolites for the production of important biomolecules such as nucleotides, lipids, glutathione, and one-carbon units. Amino acids are also oxidized in the TCA cycle as an alternative to glucose for the production of ATP and NADH. The specific amino acids which most directly contribute to these biomolecules and processes are listed. Unknown amino acids sensor(s) assess the availability of specific amino acids, likely including leucine and arginine. The Ras-like small GTPase Rag complex, modulated by the action of its GEF, Ragulator, and GAPs, tumor suppressive complexes GATOR1 and folliculin, integrate this amino acid signal and effect a change in localization of the mTORC1 complex, leading to its activation. The mTORC1 complex can then activate pathways promoting cell growth, including protein biosynthesis. Activating mutations in the mTORC1 core component mTOR, are recurrently observed in cancer. Processes exhibiting activation in cancer are colored green, tumor suppressive genes and complexes are colored orange.

sensing (Fig. 1). Moreover, alterations in the recycling of amino acids by autophagy and their scavenging from the environment by micropinocytosis of serum proteins are observed in proliferative cells, and may support the transformed state by providing amino acids during periods of starvation [7–10]. Many amino acids cannot be synthesized by the cell, and therefore their uptake is essential for protein biosynthesis and cell viability [11]. Among these essential amino acids, there is evidence that two – leucine and arginine – are sensed by the cell to determine if there is sufficient material available for protein biosynthesis [12–14]. This sensing likely occurs within or near the surface of the lysosome, and permits the activation of the mechanistic target of rapamycin complex I (mTORC1) [5]. Amino acid insufficiency provides a dominant signal to turn off the mTORC1 pathway over other inputs, such as insulin signaling, placing amino acids as key regulators of cell growth via mTORC1 [14]. Several amino acids can also be readily synthesized by the cell, and among them, serine and glutamine are consumed greatly in excess of that required for protein biosynthesis for downstream reactions providing one carbon units, TCA cycle intermediates, fatty acids, membrane lipids, and other amino acids for biosynthetic reactions [15,16]. As such, recent work has identified genetic alterations in cancer of both the machinery which senses amino acid sufficiency as well as those pathways which utilize amino acids as intermediate metabolites (Table 1). Here, we will first describe cancer-specific alterations in the use of amino acids as intermediate metabolites, followed by a discussion of the role of the mTORC1

Table 1
Alteration of amino acid management pathways in cancer.

Amino acid metabolism			
Gene	Function	Cancer alteration/relevance	References
GLS	Rate limiting step in glutaminolysis	Increased translational efficiency downstream of MYC, miR-23a/b	[58]
PHGDH	Rate limiting step in serine biosynthesis	Genomic amplification and over-expression	[23,24]
SHMT2	Diversion of serine into mitochondrial one-carbon metabolism	Over-expression, drives hypoxia resistance	[23,35,36]
GLDC	Key component of the glycine cleavage complex	Prevents toxic glycine accumulation, drives broad metabolic changes	[36,42]
ASNS	Asparagine biosynthesis	Increased expression in glioblastoma	[65]
Amino acid sensing			
Gene	Function	Cancer alteration/relevance	References
mTOR	Protein kinase, controls translation in response to nutrient sufficiency signals	Activating point mutations, amino acid starvation fails to inactivate mTORC1	[120,155]
FLCN	mTORC1 positive regulator, GTPase activating protein for RAG C/D	Loss of function mutations in Birt–Hogg–Dubé syndrome	[105–107]
DEPDC5	GATOR1 component, negative regulator of mTORC1, GTPase activating protein for RAG A/B	Deletion of 22q12.2, amino acid starvation fails to inactivate mTORC1	[116,117]
NPRL2	GATOR1 component, negative regulator of mTORC1, GTPase activating protein for RAG A/B	Deletion of 3p21.3, amino acid starvation fails to inactivate mTORC1	[116,118,119]