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Mini-review

Antagonistic role of natural compounds in mTOR-mediated metabolic reprogramming

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ABSTRACT

Cells reprogram their metabolism very early during carcinogenesis; this event is critical for the establishment of other cancer hallmarks. Many oncogenes and tumor suppressor genes control metabolism by interplaying with the existing nutrient-sensing intracellular pathways. Mammalian target of rapamycin, mTOR, is emerging as a collector and sorter of a metabolic network controlling upstream and downstream modulation of these same genes.

Natural compounds represent a source of anti-cancer molecules with chemopreventive and therapeutic properties. This review describes selected pathways and genes orchestrating the metabolic reprogramming and discusses the potential of natural compounds to target oncogenic metabolic aberrations.

1. Metabolic reprogramming as a primary event in carcinogenesis

Aberrant expression and function of specific genes (namely oncogenes and tumor suppressor genes) typically characterize early steps of carcinogenesis. Their alterations promote the deregulation of cell proliferation and cell death. Recent research evidenced that many of these genes modulate cell signaling pathways related to cell metabolism. Accordingly, defects in these genes converge into the activation of a metabolic profile typical of cancer cells, characterized by the addictive switch to aerobic glycolysis (namely the Warburg effect), increased glutaminolysis and *de novo* lipid biosynthesis as major events [1]. Current findings imply that early gene alterations during carcinogenesis may promote a process of metabolic reprogramming as a primary effect. In turn, this event might be essential for the proper establishment of other well-known cancer hallmarks. Findings support the causative modulatory role of cancer cell metabolism on sustained cell proliferation [2] and the hyperactivation of pro-survival responses [3]. Besides, there is evidence that the acquisition of the new metabolic profile may fuel other important processes typically deregulated in cancer such as inflammation [4–6] or angiogenesis [7]. According to this novel view, metabolic changes drive cancer formation rather than resulting from proliferative and pro-survival stimuli [2].

The metabolic signature of cancer cells correlates with defects in a set of genes. They encode important transcriptional factors that control expression of many metabolic enzymes or metabolites transporters. Among them phosphoinositide-3-kinase (PI3K) and Akt [8], AMP-activated protein kinase (AMPK) [9,10], c-MYC [11], p53 [12] and hypoxia-inducible factor 1α (HIF-1α) [13] are essentially implicated. They correspond to genes that are frequently mutated and/or functionally altered in cancer. Recent research advancements highlight that these factors are functionally interconnected and that the interplay among them is essential to properly coordinate cell metabolism. Evidence places the mammalian target of rapamycin (mTOR) at the crossroad of this cooperative network [13], by integrating nutrient-related signaling pathways and subsequently adapting gene expression and cell metabolism [14,15]. The existence of a multi-factorial and multi-step regulatory system of cell metabolism suggests the druggability of some

Abbreviations: AMPK, AMP-activated protein kinase; EGCG, epigallocatechin-3-gallate; CG, cardiac glycoside; 4E-BP, eukaryotic initiation factor 4E (eIF4E)-binding protein; FAS, fatty acid synthase; FoxO, forkhead box O; GLUT, glucose transporter; HK2, hexokinase-2; HIF-1α, hypoxia-inducible factor 1 alpha; HDAC, histone deacetylase; IKK, IκB kinase; IRES, internal ribosomal entry sites; mTOR, mammalian target of rapamycin; MDM-2, murine double minute 2; mTORC, mTOR complex; NF-κB, nuclear factor-κB; PPP, pentose phosphate pathway; PTEN, phosphatase and tensin homolog deleted on chromosome 10; PI3K, phosphatidylinositol-3-kinase; PFK1, phosphofructokinase-1; PKCα, protein kinase alpha; Rheb, Ras homolog enriched in brain; Rag, Ras-related GTPase; S6K, ribosomal S6 kinase; SGK, serum- and glucocorticoid-induced protein *kinase*; SREBP, sterol regulatory element-binding proteins; TSC, tuberous sclerosis complex.

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of its mediators as an attractive strategy for both chemoprevention and novel anti-cancer therapeutic approaches.

Natural compounds represent a considerable source of potential anti-cancer molecules. Among the most investigated ones, there are many compounds extracted or derived from plants, which are normally ingested with the diet [16]. They were described to target important hallmarks of cancer and most frequently correspond to anti-inflammatory [17,18], anti-proliferative and cytocidal activities [19–21].

In this review, we will focus our attention on selected pathways and genes implicated in metabolic reprogramming during carcinogenesis and we will discuss the potential of natural compounds to interfere with oncogenic metabolic aberrations.

2. Mechanisms implicated in metabolic reprogramming in cancer

2.1. mTOR as collector of multiple signaling pathways modulating cell metabolism

The serine/threonine mammalian target of rapamycin (mTOR) is a critical component of an adaptive system that senses the availability of a variety of nutrients and growth factors in the microenvironment and accordingly adapts the cellular anabolic activities. mTOR appears as a crucial controller of metabolic homeostasis. The possibility to target it by pharmacological and genetic tools offers a versatile strategy to elucidate the oncogenic and future therapeutic potential of its modulation.

Substantially, there are two distinct functional cellular pools of mTOR defined by the association with a specific set of binding proteins (Fig. 1). mTOR complex 1 (mTORC1) interacts with its specific regulator Raptor and is the preferential target of the macrolide rapamycin [22]. Direct substrates of mTORC1 include the ribosomal S6 kinases (S6K) and the eukaryotic initiation factor 4E (eIF4E)-binding protein 1 (4E-BP1) [14,15]. Upon mTOR-dependent phosphorylation, they are activated and inhibited, respectively and thereby promoting mRNA translation by different mechanisms [14]. mTOR complex 2 (mTORC2) is regulated by Rictor and its known substrates are the serum- and glucocorticoid-induced protein kinase (SGK) and the protein kinase alpha (PKCα) [15] (see Table 1).

The direct role played by mTORC1 in biosynthetic processes together with the availability of selective pharmacological inhibitors [22] intensified investigation of this complex [15]. Suppression of

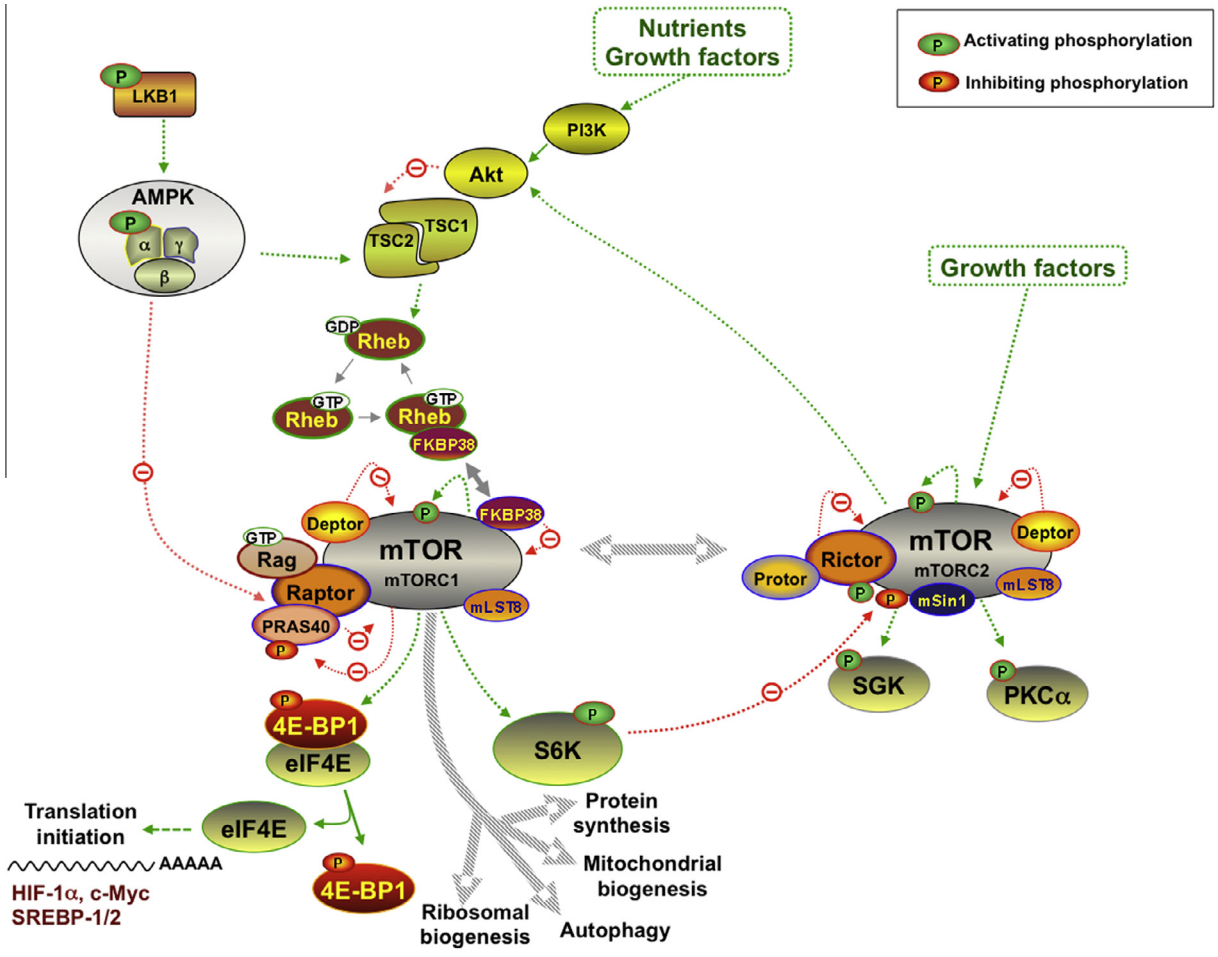

Fig. 1. Protein partners and modulation of mTOR. The interaction of the protein serine/threonine kinase mTOR with other protein partners defines two distinct functional complexes. The mutual modulations among components of each complex or between the two major complexes mTORC1 and mTORC2 are here schematized. mTORC1 complex includes the critical positive regulator Raptor, the two negative regulators PRAS40 and DEPTOR besides the protein SLT8 whose function remains undetermined. mTORC2 contains as critical modulators, the protein Rictor besides the positive regulator mSIN1 and the negative regulator DEPTOR; additionally, the complex contains also the proteins SLT8 and Protor whose modulatory functions are still under investigation. Modulation of mTORC1 is based on GTPase activities mediated by the small GTPase Ras homolog enriched in brain (RHEB) or, as in the case of amino acid-dependent signaling, Ras-related GTPase (Rag). In both instances, promotion of their GTPase activity signals the inactivation of mTORC1. RHEB is the downstream effector of activated PI-3K/Akt or AMPK, both modulating the GTPase TSC-2 in an opposite way as schematized. The inhibitory protein FKBP38, which binds mTOR in proximity to its catalytic domain, is implicated in RHEB-mediated modulation. AMPK may act also on Raptor (by phosphorylation) leading to suppression of mTORC1 activity [93]. This scheme was generated with ScienceSlides.

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