INTRACELLULAR MECHANISMS OF NATURAL SUBSTANCES INVOLVED IN THE REGULATION OF CELL SURVIVAL AND APOPTOSIS: A REVIEW

Zuzana Baková*, Nora Maruniaková, Sushmita Nath, Adriana Kolesárová

Address: 1Slovak University of Agriculture in Nitra, Faculty of Biotechnology and Food Science, Department of Animal Physiology, Tr. A. Hlinku 2, 949 76 Nitra, Slovak Republic
2Sushmita Nath, M.Sc. Life Science (Zoology); PGDBI, Assam University: Silchar, Ethnobotany and Medicinal Plant Research Laboratory, Department of Life Science and Bioinformatics, 788011 Silchar, India

*Corresponding author: Zuzana.Bakova@yahoo.com

ABSTRACT

Natural substances which are considered to be a food or part of a food that provides medical and health benefits are called nutraceuticals. Resveratrol is one of such substances that signify potential benefit as anti-carcinogenic, lowering of blood sugar level, anti-inflammatory, antioxidant and cardioprotective properties in various types of cells and animal models including inhibition of PI3K/AKT/mTOR pathway. Activation of PI3K/Akt/mTOR pathway plays a pivotal role in essential cellular functions such as survival, proliferation, migration and differentiation in various types of cells. As the in vivo functions of mTOR remain elusive is possible that mTOR plays more important roles than had been anticipated from studies.

Keywords: natural substances, mTOR pathway, resveratrol
INTRODUCTION

The relationship between nutrition and physiological processes has been the aim of interest to physiologists since the end of the 19th century (Heape, 1899; Marshall, 1904). In recent years considerable effort has been made to identify the metabolic and nutritional factors linking nutrition with partial physiological processes (Monget and Martin, 1997; Kolesárová et al., 2011).

Nowadays, the study of natural substances with pharmacological activity, such as flavonoids, has become an emerging trend in nutritional and pharmacologic research. Numerous data from various mammalian species have shown that nutrition may influence the physiological functions including the reproductive efficiency (Prunier and Quesnel, 2000), tumorigenesis (Subash et al., 2010), carcino genesis, angiogenesis, cell survival, proliferation and invasion (Subash et al., 2010; Aggarwal et al., 2009). Natural substances which are considered to be a food or part of a food that provides medical and health benefits are called nutraceuticals (a term formed by combining the words “nutrition” and “pharmaceutical”) (Brower, 1998; Zeisel, 1999).

Most experimental studies involving farm animals have focussed on the negative consequences of undernutrition on reproductive performance (Prunier and Quesnel, 2000). Ovarian activity, growth of antral follicles, ovulation rate, delay of puberty and returning to oestrus after weaning in farm animals is influenced by nutrition and body reserves (Downing and Scaramuzzi, 1991; Prunier and Quesnel, 2000).

Oocyte maturation and hence the number of viable embryos per litter can be also affected by nutrition. Plant phenolics presented in fruit and vegetables and particularly in red wine, have received considerable attention because of their potential antioxidant (López-Vélez et al., 2003), anti-carcinogenic (Wang et al., 2003; Jiang et al., 2005), anti-inflammatory (Liu et al., 2010) and cardioprotective activity (Soleas et al., 2006).

Multiple apoptotic signaling cascades may be activated by naturally occurring flavonoids, including resveratrol, from which Phosphatidylinositol 3-kinases/Akt protein kinase/ Mammalian target of rapamycin (PI3K/Akt/mTOR) signaling pathway is an important signaling cascade involved in the regulation of cell growth and proliferation in a various types of cells (Teiten et al., 2010; Brito et al., 2009).
Resveratrol

Resveratrol (trans-3,5,4’-trihydroxystilbene) (Fig 1) is a naturally occurring polyphenol structurally related to stilbenes (Rocha-Gonzáles et al., 2008) synthesized by plants as a phytoalexin that protects against ultraviolet radiation and fungal infection (Mukherjee et al., 2010; Jiang et al., 2005). Resveratrol occurs in two isoforms cis- and trans- resveratrol, but trans- resveratrol is more biologically active than its cis isoform (Mukherjee et al., 2010). It is found in high concentration in natural foods such as grapes, mulberry, lingberry, bilberry, nuts, blueberries, red grapes, wine (Das and Maulik, 2006) and by at least 72 medicinal and edible plant species in response to stress conditions (Rocha-Gonzáles et al., 2008).

The fact that resveratrol is contained in a wide variety of dietary resources gives a reason to think that regular consumption of resveratrol in the diet may be useful for treatment of multiple illnesses in which it has shown pharmacological activity (Rocha-Gonzáles et al., 2008). Resveratrol signify potentially beneficial anti-carcinogenic (Athar et al., 2009; Shankar et al., 2007ab; Polans, 2007; Jiang et al., 2007; Aggarwal, 2010), blood-sugar-lowering (Mukherjee et al., 2010), cardioprotective (Das and Maulik, 2006), anti-inflammatory (Jiang et al., 2005), chemoprotective (Shankar et al., 2007ab; Sluszar et al., 2010; Wu et al., 2010; Bai et al., 2010; Harikumar et al, 2010; Lee et al., 2009; Li et al., 2009) and antioxidant (Hattori et al., 2002) activities in various types of cells and animal models. Most likely the in vivo antioxidant property of resveratrol is derived from its ability to increase nitric oxide (NO) synthesis, which in turns acts as an antioxidant. It has been shown that resveratrol induces NO synthesis in case of ischemic reperfused heart, brain and kidney and lower the oxidative stress (Hattori et al., 2002; Cadenas and Barja, 1999). Resveratrol has also been shown to exhibit profound in vitro and in vivo growth-inhibitory and apoptosis-inducing activities in several cancer cell lines and animal models of carcinogenesis and tumorigenesis (Joe et al., 2002; Jiang et al., 2007). These properties have been linked to the inhibition of proliferation in association with cell cycle arrest and apoptotic cell death typically observed in vitro (Joe et al., 2002; Sun et al., 2006; Van Ginkel et al., 2010; Jiang et al., 2005). In addition, resveratrol also exerts its effects by interacting with multiple cellular targets and modulating various signal transduction pathways (Athar et al., 2009). To further examine the effect of resveratrol on mammalian target of rapamycin (mTOR) human U251 glioma cells were treated with resveratrol. The results suggest that resveratrol decreases the activation of Akt/mTOR and inhibition of mTOR by rapamycin further enhances the resveratrol-induced apoptosis (Jiang et al., 2005). Other authors suggest that resveratrol is
able to inhibit PI3K/Akt/mTOR pathway in various types of cells (Shankar et al., 2007ab; Bai et al., 2010; Srivastava et al., 2010).

**Figure 1** Isoforms trans-resveratol and cis-resveratrol (Melzoch et al., 2000)

**mTOR signaling pathway**

The hormonal control of particular physiological processes uses a number of distinct and sometimes interconnected signaling pathways (Kesari et al., 2005; Bjornsti and Houghton, 2004). In mammalian cells, mTOR is a large polypeptide kinase that acts as a nutrient sensor and regulator of translation (Schmelzle and Hall, 2000; Kesari et al., 2005; Bjornsti and Houghton, 2004; Dutcher, 2004; Fingar et al. 2004) and proliferation by controlling cell growth or acting directly on the phosphorylation cascade that controls cell cycle regulatory proteins (Fingar et al. 2004). Activation of PI3K/Akt/mTOR pathway plays a pivotal role in essential cellular functions such as survival, proliferation, migration and in various types of cells (Dancey, 2004; Teiten et al., 2010). The stimulation of this pathway begins with the activation of receptor tyrosine kinases, which promotes the recruitment and activation of PI3K family members. PI3K phosphorylates phosphoinositides (PIPs) at the 3-hydroxyl of the inositol ring. These phosphorylated phospholipids (PI3Ps), act as membrane tethers for many PI3K downstream effector proteins with pleckstrin homology (PH) regions (Storz and Toker, 2002). PI3Ks can additionally be activated by signaling mediated by G-protein coupled receptors and Ras (Katso et al., 2001). Upon activation, PI3Ks phosphorylate phosphatidylinositol-4,5-bisphosphate (PIP2) to convert it to phosphatidylinositol-3,4,5-trisphosphate (PIP3), a process opposed by phosphatase and tensin homolog (PTEN) (Carracedo et al., 2008). Effector proteins phospholipid-dependentkinase 1 (PDK1) and Akt are activated through the binding of their PH domains to lipid products of PI3K on the plasma membrane. PDK1 is a serine/threonine protein kinase that phosphorylates several members of the conserved AGC kinase superfamily [comprising the prototype protein kinases A (PKA), B
Phosphorylation of Akt and mTOR is significantly correlated, and deregulation of PI3K/Akt/mTOR signaling may lead to uncontrolled protein synthesis and cell cycle progression (Kesari et al., 2005).

**SUMMARY, CONCLUSIONS, AND FUTURE PERSPECTIVES**

Although data from several studies dealing with molecular mechanisms through natural substances effect the cells were obtained, several open questions remain still unknown. The mTOR signaling network is likely to be very complex, including crosstalk and feedback mechanisms. Agents that inhibit the downstream protein kinase mTOR as well as agents that inhibit multiple kinases including components of the PI3K-Akt pathway are under clinical evaluation. Nowadays, natural substances, including resveratrol, occur to be able to effect cell processes through PI3K/Akt/mTOR signaling pathway.

**Acknowledgments:** Our research was supported by VEGA scientific grant no. 1/0790/11 and no. 1/0084/12.

**REFERENCES**


HARIKUMAR, K. B. - KUNNUMAKKARA, A. B. - SETHI, G. - DIAGARADJAN, P. - ANAND, P. - PANDEY, M. K. - GELOVANI, J. - KRISHNAN, S. - GUHA, S. -


