



Ribosomal Protein S6 Phosphorylation in the Nervous System: From Regulation to Function

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Since the discovery of the phosphorylation of the 40S ribosomal protein S6 (rpS6) about four decades ago, much effort has been made to uncover the molecular mechanisms underlying the regulation of this post-translational modification. In the field of neuroscience, rpS6 phosphorylation is commonly used as a readout of the mammalian target of rapamycin complex 1 signaling activation or as a marker for neuronal activity. Nevertheless, its biological role in neurons still remains puzzling. Here we review the pharmacological and physiological stimuli regulating this modification in the nervous system as well as the pathways that transduce these signals into rpS6 phosphorylation. Altered rpS6 phosphorylation observed in various genetic and pathophysiological mouse models is also discussed. Finally, we examine the current state of knowledge on the physiological role of this post-translational modification and highlight the questions that remain to be addressed.

Keywords: rpS6 phosphorylation, mRNA translation, ribosome, mTOR, S6K, PP-1, brain, signaling cascades

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INTRODUCTION

The eukaryotic ribosome is composed of the small 40S and the large 60S subunits, comprising together 4 ribosomal RNA species and 79 ribosomal proteins (Kressler et al., 2010). In many organisms, ribosomal proteins undergo various post-translational modifications, including phosphorylation, acetylation, methylation, O-linked β -N-acetylglucosaminylation, and ubiquitylation (Xue and Barna, 2012). Historically, the phosphorylation of the 40S ribosomal protein S6 (rpS6) was the first post-translational modification described (Gressner and Wool, 1974). The presence of phospho-rpS6 (p-rpS6) at different levels in a 2D gel provided the first evidence that rpS6 phosphorylation could occur at several residues (Lastick et al., 1977). Ensuing studies identified five evolutionary conserved and clustered carboxy-terminal phospho-sites, which undergo phosphorylation in an ordered manner, beginning with Ser236 and followed sequentially by Ser235, Ser240, Ser244, and Ser247 (Martin-Pérez and Thomas, 1983; Wettenhall et al., 1992; Meyuhas, 2008, 2015). Intriguingly, the exact function of the post-translational modification of this indispensable ribosomal protein remains enigmatic. Despite the large debate regarding its physiological role, rpS6 phosphorylation is commonly used as a marker for neuronal activity and a readout of mammalian target of rapamycin complex 1 (mTORC1) activity (Meyuhas, 2008, 2015; Mahoney et al., 2009; Knight et al., 2012). This review summarizes our current knowledge regarding the molecular mechanisms as well as the variety of stimuli modulating rpS6 phosphorylation in the nervous system.

Protein Phosphorylation In The Nervous System

N Colangelo



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