PICK1 Deficiency Impairs Glutathione Synthesis and Increases Oxidative Stress via Reduction of Surface EAAC1

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**Abstract:** Protein interacting with C-kinase 1 (PICK1) has received considerable attention, as it interacts with a broad range of neurotransmitter receptors, transporters and enzymes, and thereby influences their localization and function in the central nervous system. Although it is suggested that putative partners of PICK1 are involved in neurological diseases such as schizophrenia, Parkinson’s disease, chronic pain, and amyotrophic lateral sclerosis, the functions of PICK1 in neurological disorders are not clear. Here, we show that oxidative stress, which is tightly associated with neurological diseases, occurs in PICK1-/- mice. The oxidation in PICK1-/- mice was found selectively in neurons and was age-dependent, leading to microglial activation and the release of inflammatory factors. Neurons in the cortex and hippocampus from PICK1-/- mice showed increased vulnerability to oxidants and reduced capacity to metabolize reactive oxygen species; this was caused by reduced glutathione content and impaired cysteine transport. The dysregulated expression of glutathione was attributed to a decrease of the surface glutamate transporter EAAC1. Overexpression of PICK1 could rescue the surface expression of EAAC1 and ameliorate the glutathione deficit in PICK1-/- neurons. Finally, reduced surface EAAC1 was associated with defective Rab11 activity. Taken together, these results indicate that PICK1 is a crucial regulator in glutathione homeostasis and may play important roles in oxidative stress and its associated neurodegenerative diseases.

**Key words:** PICK1; oxidative stress; EAAC1; glutathione; Rab11; oxidant

**个人简介：**

沈颖，浙江大学教授，博士生导师。取得的工作成绩包括：A，首次详细分析了 视网膜中谷氨酸受体的亚型组成和在视网膜光信号转导中的作用。B，证实了小脑中的一个新型突触可塑性模型，并且首次以可靠的实验证明了其表达的位置。C，首次报道了神经元型谷氨酸转运体的可塑性，并且提出可能与PKC、mGluR等胞内代谢途径相关。D，首次提出SRF，而不是以往广泛关注的CREB，可能对海马LTP起关键作用。已经在包括Nature Neuroscience, Neuron, PNAS, Journal of Neuroscience, Glia在内的国际顶尖杂志上发表研究论文。主要研究方向：1）小脑突触传递和可塑性机制；2）髓鞘发育和脱髓鞘疾病。

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