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| • 英文摘要 | Methylprednisolone (MP), a synthetic glucocorticoid (GC), is the only proven therapeutic agent for acute spinal cord injury (SCI). MP, like other GCs, has broad effects on transcription factors including those affecting cell viability and those causing serious adverse side effects. In this project, we elucidated two novel genetic mechanisms that underlie MP protection of oligodendrocytes (OLGs) against death signals in vitro and in vivo. The first is the transactivation of bcl-xL, an anti-apoptotic gene, via Stat5. Promoter analysis of the bcl-xL gene delineated a GC-responsive promoter region. Using mice overexpressing Stat5, the causal role of Stat5 in this GR-meidated transactivation of bcl-xL expression was confirmed. The second genetic mechanism of MP neuroprotection is the transactivation of erythropoietin (EPO), a neuroprotective gene, via hypoxia inducible factor (HIF). For MP transactivation of EPO gene expression, a GC-responsive promoter region containing HIF response element (HRE) was identified.. RNAi techniques were extensively applied in this project to elucidate the pivotal role of HIF-1, the inducible component of HIF that binds to HRE for transactivating EPO gene expression. Results show that the activity of GC-responsive hEPO enhancer was abolished by HIF-1？？ and GR siRNA. Furthermore, we found that MP activation of HIF-1 involved a novel protein-protein interaction. A high throughput molecular modeling system combined with conventional yeast-2-hybrid and immuno co-precipitation were applied to confirm direct interactions between GR and HIF-1. These in vitro findings were further confirmed in in vivo |

experiments using rodent SCI models. The neuroprotecitve mechanisms of MP based on bcl-xL and EPO transactivation involving 2 different transcription factors (Stat5 and HIF) and the related proteomics models will be applied to establish high throughput systems for identifying ideal GCs to optimize the neuroprotective mechanisms of MP while minimizing the broad actions of GCs that are associated with serious adverse side effects, especially when used for extended period of time.