

DOI: 10.21767/2172-0479.100062

# A Novel Tissue Protective Peptide: Cyclic Helix B Peptide

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## Introduction

Renal transplantation is one of the best choices for the treatment to the end stage renal disease. However, the shortage of the donor organs is a worldwide challenge, and the huge demand for transplantation forced the widely use of organs from expanded criteria donors or donation after cardiac death. Kidneys from these donors are highly sensitive to ischemia reperfusion (IR) injury, which might cause delayed graft function and affects both short- and long-term graft survival. Since IR injury is inevitable during kidney transplantation, it is urgent to develop an effective drug to optimize the organ preservation and ameliorate the tissue injury.

Erythropoietin (EPO) is an endogenous protein that exerts tissue-protective effects for a wide range of organs, but the very high dosage required to achieve that goal would cause unfavorable side effects, including hypertension and thrombosis [1-3]. Helix B surface peptide (HBSP), which was derived from the aqueous surface of the helix B domain of EPO, was found to exert powerful tissue-protective function against IR injury without the ability of erythropoiesis [4,5]. However, this 11-amino acid protein is easily metabolized by the protease and its half-life is only 2-minute *in vivo*, which restricts its application [4].

Based on the structure of HBSP, our group firstly synthesized a novel proteolysis-resistant cyclic helix B peptide (CHBP) with improved metabolic stability and tissue-protective potency [6]. It was shown that CHBP significantly ameliorated inflammation in renal IR injury in a murine model, in terms of decreased apoptosis, pro-inflammatory cytokines expression and complement activation [6]. The main mechanism is the binding to the tissue protective receptor (TPR), which is a heterodimer receptor composed of EPO receptor (EPOR) and  $\beta$  common receptor ( $\beta$ cR), and then the downstream signaling pathway of Jak-2/STAT3 is activated [7,8]. Besides, we identified CHBP-induced autophagy through activation of AMPK and inhibition of mTOR complex 1 (mTORC1) in the IR injury kidney for the first time, which also contributed to its renoprotective effects [6]. We further proved that the administration of CHBP into preservation solution and autologous blood perfusate ameliorated IR injury in isolated porcine kidney by increasing renal blood flow and oxygenation and reducing apoptosis and

inflammation, which suggested the promising application of CHBP in organ preservation [9].

IR injury of kidney is a well-established cause of renal fibrosis in long-term [10]. CHBP not only ameliorates the tissue injury of IR, but also attenuates fibrosis after IR through inhibition of TGF- $\beta$ -induced extracellular matrix protein expression and epithelial-mesenchymal transition in tubular epithelial cells. The mechanism mainly involves the suppression of PI3K/Akt pathway and subsequent inhibition of FoxO3a [11]. In addition, CHBP also plays a role in immune regulation. It was revealed that CHBP suppressed dendritic cell (DC) maturation via the activation of Jak-2/STAT3/SOCS1 signaling pathway, which subsequently inhibited the activation of toll-like receptor (TLR). As a result, the CHBP-induced immature DC ameliorated acute rejection in a rat kidney transplantation model [8].

Actually, IR injury is not confined to the transplantation, but quite common in many pathophysiologic situations, including acute kidney injury, acute coronary syndrome etc. Since the multiple tissue-protective functions of CHBP, it is a promising drug in many fields. What's more, the evolution from EPO to CHBP results from the creative innovation, and shares the scientific methods with other drug development.

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