

## Introduction

Respiratory insufficiency is the leading cause of morbidity and mortality after traumatic cervical spinal cord injury (SCI). In contrast to acute and traumatic SCI, non-traumatic spinal cord injury (ntSCI) as in cervical myelopathy (CSM) results in subclinical and mild respiratory dysfunction despite significant disruption of the cervical neural network. This study seeks to understand the mechanism of this respiratory plasticity in ntSCI and investigates a novel therapeutic strategy to restore breathing immediately after SCI.

## Methods

ntSCI was modeled in the form CSM to examine the status of cervical respiratory network. Phrenic motoneurons (PMNs) and cervical interneurons were retrogradely traced via cholera toxin b (CTb) and pseudorabies technology, respectively. Excitatory input onto PMNs were examined using vesicular glutamate transporter 2 (Vglut2)+ boutons on PMNs. To confirm the role of cervical glutamatergic neurons in promoting respiratory plasticity and breathing in ntSCI and chronic SCI, we injected AAV-FLEX-PSAML141F-GlyR-IRES-eGFP in the ventromedial area of C3-5 spinal levels of Vglut2::cre mice two week prior to the induction of ntSCI and SCI. Finally, we examined the efficacy of pharmacogenic stimulation of these cervical glutamatergic neurons in restoring breathing immediately after traumatic SCI.

## Results

Using a combination of pharmacogenetics and respiratory physiology assays in spinal cord injury (ntSCI and SCI), we show that midcervical excitatory interneurons are essential for the maintenance of breathing in ntSCI and critical for promoting respiratory recovery after traumatic SCI. Importantly, stimulation of cervical excitatory interneurons following traumatic SCI was sufficient to rescue breathing in mice at the acute stage, the most critical period for SCI patients.

## Conclusions

This is the very first study demonstrating a strategy to restore breathing immediately after traumatic high cervical SCI. In future, viral vectors can potentially be used to target this subpopulation in humans with SCI.

## Learning Objectives

1. Understand the role of cervical excitatory interneurons in breathing
2. Explore potential ways of manipulating this population of neurons to restore breathing in SCI patients

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