



## 【校級神經醫學研究中心 110 年 8 月份月會】 會議紀錄

時 間：110年8月11日(星期三) 12:10-13:30  
地 點：視訊會議-Google Meet  
主 席：蔣永孝 主任(王家儀 執行長代理)

### TMU Neuroscience Research Center Monthly Meeting Record for August, 2021

**Chair:** Prof. Jia Yi Wang

Recorded by: Professor J. Y. Wang,  
Secretary C. N. Huang

**Host:** The Traumatic Brain Injury Team

**Time:** 2021/8/11 (Wednesday) 12:10-13:30

**Place:** Net meeting via Google Meet

#### Meeting Agenda (議程) :

1. Opening by Prof. Jia Yi Wang 王家儀執行長
2. “Eph/ephrin Signaling in Neural Circuit Formation and Its Implication in mTBI” presented by Dr. Tzu-Jen Kao 高祖仁副教授

## 1. Opening

In the opening, Prof. Wang first welcomed Dr. Tzu-Jen Kao from the Traumatic Brain Injury Team to share his research with us today. Dr. Kao completed his Ph.D. degree in medicine at the University of South Carolina and now is an associate professor in the Ph.D. Program for Neural Regenerative Medicine at TMU. His research focuses on axon guidance, developmental neuroscience, and cell biology. 王家儀執行長首先歡迎腦創傷團隊的高祖仁老師今天來跟我們分享他的研究。高老師畢業於美國南卡羅來納大學並取得生物醫學博士學位，目前是神經再生醫學博士學位學程的副教授。他的主要研究領域在軸突引導、發育神經學及細胞生物學。

## 2. Forum hosted by the Traumatic Brain Injury Team

### 1) Eph/ephrin Signaling in Neural Circuit Formation and Its Implication in mTBI by Dr. Tzu-Jen Kao

Brief summary of Dr. Kao's speech:

During the development of functional neural circuits, neuronal growth cones must be guided precisely to their neuronal or muscle targets, which can be achieved by activating membrane-bound guidance receptors located at the periphery of the growth cones. Among these guidance receptor/ligand families, Eph tyrosine kinase receptors and their ephrin ligands have been proposed to mediate the proper axon trajectory of at least several neuronal types. However, several issues, including 1) how Eph receptors relay their signals to the cytoskeleton to mediate growth cone turning and 2) mechanisms that regulate the temporal availability of

these receptors, remain largely unknown, which prompt us to identify the key Eph intermediaries and its candidate regulators in the context of axon guidance of the spinal lateral motor column (LMC) neurons into the limb mesenchyme. In addition, due to Eph/ephrin's potential roles in traumatic brain and spinal cord injury, we also started to examine **3**) the involvement of Eph/ephrin signaling in brains following the mild traumatic brain injury (mTBI).

We first identified the expression of several potential Eph intermediaries, including ephexin1, a Rho GTPase modulation protein, and paxillin, a focal adhesion protein, in both mouse and chick LMC motor neurons at the developmental stage when axons grow into the limb. Both ephexin1 and paxillin loss- and gain-of-function using *in-ovo* electroporation in chick LMC neurons perturbed LMC axon trajectory selection demonstrating their essential roles in motor axon guidance. In addition, both ephexin1 and paxillin deletion in mice led to LMC axon trajectory selection errors. We also show that knocking down ephexin1 and paxillin attenuates the growth preference of LMC neurites against ephrins *in vitro*, and Eph-mediated retargeting of LMC axons *in vivo*, suggesting ephexin1 and paxillin involvement in Eph-mediated LMC motor axon guidance.

TAR DNA binding protein-43 (TDP-43) belongs to the heterogeneous nuclear ribonucleoprotein family that functions as a versatile DNA/RNA binding protein and has been proposed to bind with the mRNAs of several guidance receptors, including Eph members. To investigate its role in modulating Eph translation in the context of LMC pathfinding, we first identified the TDP-43 expression in the LMC neurons. The loss and gain of *TDP-43* function in chick LMC neurons redirect their axon trajectory with opposite effects. In mice, a spinal motor neuron-specific *TDP-43* deletion led to the misrouting of the LMC axons. Further, ectopic *TDP-43* expression increases EphB protein levels in LMC neurons, suggesting that TDP-43 mediates LMC pathfinding by regulating EphB expression.

To investigate the involvement of Eph signaling in mTBI, we first examined the expression of Eph and ephrin in mouse following mTBI and found the elevated expression of members of Eph and ephrin in brains with mTBI compared with untreated mice. In addition, we also observed that the expression of both Eph intermediaries, paxillin and ephexin1, and the Eph regulator, TDP-43, were increased in brains with mTBI, thus implying Eph/ephrin involvement in mTBI. Further investigation of Eph signaling with either loss or gain of function experiments will be required to clarify the role of Eph signaling in this context.

**Eph signaling in LMC pathfinding**

Development/Plasticity/Repair  
**Src Family Kinases Are Required for Limb Trajectory Selection by Spinal Motor Axons**

Tzu Jen Kao, Elena Palmelino, and Artur Kania<sup>1,2</sup>  
<sup>1</sup>Unité de recherche clinique de Neurosciences, Institut Québécois de Recherche sur le cerveau, Université de Montréal, Montréal, Québec H3C 3J7, Canada; <sup>2</sup>Department of Anatomy and Cell Biology, Division of Experimental Medicine, McGill University, Montreal, Quebec H3A 2B4, Canada; and <sup>3</sup>Faculté de médecine, Université de Sherbrooke, Sherbrooke, Québec J1K 0R2, Canada

**Experimental Design**

- Loss-of-function experiments:**
  - chick: knockdown by expressing siRNA
  - mouse: *paxillin* mutant
- Gain-of-function experiments:**
  - Over-expression of *paxillin* plasmids
- In vitro stripe assay (離體條紋分析法)**

motor neuron explant/stripe co-culture  
 chick at 300h spinal cord  
 18 hr

Kao and Kania, Neuron 2011

Brain-body interactions in perception and action presented by Dr. Tzu-Jen Kao (8/11, 2021)

## 2) Discussion

Academician Che-Kun Shen (沈哲鯤院士) and Dr. Chung-Che Wu (吳忠哲醫師) discussed the research result with Dr. Kao. Jiann-Her Lin (林建和醫師) also asked why Dr. Kao choose EPH for TBI and what is Dr. Kao's expectation for the role of the EPH in TBI. Dr. Kao said that because he is working on the EPH signal so he was trying to apply the EPH signal to the injury. He found the TBI and some neural degenerate diseases are related to the EPH signal. The increase of EPH and ephrin is not only seen in the TBI, but also in the spinal cord injury. The ephrin increase or EPH increase is specific only seen in only restricted in the injury site, so because of the EPH and ephrin interaction which is repulsive. They think that's one of the reasons why the broken nerve or the injured nerve cannot regenerate, due to the repulsive interaction between the axon express the EPH and the high ephrin expression in the high injury site. Dr. Kao also mentioned another literature, they are trying to decrease or inhibit, the EPH expression or the activities, and see whether that can improve the recovery of traumatic brain injuries. Therefore, in the future, Dr. Kao will plan to use combined treatment, not only

to inhibit the activity of EPH or ephrin but also their downstream intermediary, and see if or not they further, improve the recovery of those animals with the brain injuries.

會議結束時間為 13:20。