

(Form: Century 11 point, A4 size)

## Report of "Research Award of Oral Sciences"

Major: Oral Sciences

Grade: 4

Department: Orthodontics and Dentofacial  
Orthopedics

Name: Islamy Rahma Hutami

Title: Hypoxia inducible factor-1 $\alpha$  regulates the palatal wound healing via M1/M2 macrophage reprogramming.

### 1. Aim of research and results obtained (Approximately 400 words):

It has been well-documented that oral mucosa wounds heal faster than skin wounds. Nevertheless, following surgical closure in the palatal tissue, wound healing impairment and scar tissue formation typically occur. The blood flow in the wound scar region is known to be decreased compared to the surrounding area of the wound closure. Hypoxia-inducible factor -1 $\alpha$  (HIF1 $\alpha$ ), a key programmer of metabolism in inflammatory cells, is known to trigger macrophages recruitment and activation. However, the regulation of M1/M2 macrophages in palatal wound healing within HIF1 $\alpha$  deficiency condition remains unclear. Here, we investigated the role of HIF1 $\alpha$  signaling on M1/M2-like macrophage expression of heterozygous HIF1 $\alpha$ -deficient (HIF1 $\alpha$  Het) mice palatal wound healing.

HIF1 $\alpha$ -Het mice (n=40) and its wild-type (WT) littermates (n=40) were used. Wound preparation and histological analyses were performed to assess the palatal wound closure. RNA isolations from palatal tissue surrounding the wound area, dermal fibroblast, and bone marrow macrophages (BMMs) were carried out. Immunoblot analysis was used to analyze the M1/M2 and mitogen-activated protein-kinase expression. Immunohistochemical analyses were performed to analyze the macrophage infiltration.

Histological examination revealed that palatal wound closure was delayed in HIF1 $\alpha$ -Het mice compared with WT mice. In a wound scratch assay, primary fibrocytes isolated from skin and transfected with an HIF1 $\alpha$  targeting siRNA

exhibited a greater decrease in cell motility and fibroblast products than the control cells. The production of monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1 $\alpha$  (MIP-1 $\alpha$ ) was diminished in HIF1 $\alpha$ -Het mice compared with WT mice. These results indicate that HIF1 $\alpha$  deficiency may regulate the recruitment of inflammatory cells during the palatal wound healing.

Moreover, HIF1 $\alpha$  deficiency depressed the infiltration of M1/M2-like macrophage markers (iNOS, TNF- $\alpha$ , Arginase-1, CD163) and the sphingosine-1-phosphate (S1P)-receptor 1 (S1P<sub>1</sub>) expression was increased in the palatal wound of HIF1 $\alpha$ -Het mice compared with WT mice. Furthermore, immunoblot analysis from BMMs treated with S1P showed a greater decreased expression of phosphorylation p38, Akt, and ERK in HIF1 $\alpha$ -Het mice than in WT mice. These results suggest that HIF1 $\alpha$  signaling pathway plays an important role through the regulation of M1/M2 macrophage in the palatal wound healing.

## 2. Self-evaluation of research achievement:

I deeply thank Tokushima University Graduate School of Oral Science for their generosity in giving me a gold winner of “the Research Award of Oral Sciences”. Under the financial support of “the Research Award of Oral Science”, I attended the Association of Orthodontists (Singapore) Congress (AOSC) 2019 meeting in Marina Bay Sands, Singapore and joined the scientific poster competition held by this program. The competition was very tough, there were 3 judges who are Professor of Orthodontics from various countries and the competitors came from several countries in Asia Pacific. Fortunately, I got the first award for the research category of the poster competition.



3. Meeting presentation:

\* Title, conference, venue, date, co-author, presentation (oral/ poster).

(Underline the speaker.)

- Title: Hypoxia inducible factor-1 $\alpha$  regulates the palatal wound healing via M1/M2 macrophage reprogramming. Association of Orthodontics (Singapore) Congress (AOSC). Marina Bay Sands, Singapore. February 22-24, 2019. Islamy Rahma Hutami, Hiroki Mori, Tanaka Eiji, and Takashi Izawa. Poster presentation.

※Please mention about only meeting presentations and journal publications which are related to the “Research Award of Oral Science.”

For example;

- The presentations and publications with this award’s support.
- The presentations and publications was made by some supplies that you bought from this award’s money.