

## 論文審査の要旨

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### A Switch in the Dynamics of Intra-platelet VEGF-A from Cancer to the Later Phase of Liver Regeneration after Partial Hepatectomy in Humans

(肝細胞癌に対する肝部分切除後の再生過程における 血小板 VEGF-A の役割の 2 面性)

Liver regeneration is a complex process that involves several signaling cascades including intercellular interactions via different growth factors and cytokines. Platelets role in liver regeneration has been known for last few years. There are several molecular and clinical data providing evidences of platelet contribution in liver regeneration after partial hepatectomy in experimental models and humans. However, the precise mechanism is not yet known. Applicant has reported a prospective trial on the role of intra-platelet (IP) VEGF-A in the angiogenic phase of hepatic regeneration after partial hepatectomy in patients with hepatocellular carcinoma (HCC). In 37 patients with HCC undergoing both minor and major liver resections, IP VEGF-A was assessed both preoperatively and postoperatively after 4 weeks. The pattern of change in IP VEGF-A concentration was analyzed between major and minor hepatectomy groups on the basis of tumor volume and residual liver volume after partial hepatectomy. Additionally, serum interleukin-6 (IL-6) concentration and its association with IP VEGF-A were analyzed. The profile of soluble VEGF receptors during liver regeneration was also included in the study. Concentration of growth factors and cytokines were measured using the ELISA system. In order to identify the residual liver volume, a three-dimensional volume analyzer based on computed tomography (CT) scan was used.

As a result, this study has revealed the following clinical and molecular evidences.

1. Concentration of serum and IP VEGF-A was significantly elevated postoperatively at the later phase after partial hepatectomy compared to the preoperative level.
2. Pre and postoperative serum and IP VEGF-A concentration were higher in major hepatectomy group compared to minor.
3. The concentration of IP VEGF-A was based on tumor volume and residual liver volume after partial hepatectomy.
4. Serum IL-6 was significantly elevated postoperatively and positively correlated to IP VEGF-A concentration.
5. Soluble VEGF receptor-1 was distinctly suppressed at the later phase of liver regeneration.

This study has identified a marked increase of IP VEGF-A during later phase of liver regeneration. Angiogenesis is a crucial event for the maintenance and progression of liver regeneration. By identifying the feature of IP VEGF-A during liver regeneration, this study has served an important finding in understanding angiogenesis during liver regeneration. Through this study, applicant has demonstrated how IP VEGF-A maintains and switches its dynamics from cancer to liver regeneration. These findings will be vital to further investigate platelets role as an inducer of liver regeneration in angiogenic phase of liver regeneration. よって本研究は学位論文として十分な価値を有するものと判定した。