最終試験の結果の要旨

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主査および副査の５名は、平成 28 年 6 月 14 日、学位申請者 アリアル ビベック君に面接し、学位申請論文の内容について説明を求めると共に、関連事項について試問を行った。具体的には、以下のような質疑応答がなされ、いずれについても満足すべき回答を得ることができた。

質問１）How IP VEGF-A accumulates in liver after partial hepatectomy?

回答）Platelets are known to accumulate in liver after partial hepatectomy which is thought to be the result of hemodynamic alteration following hepatectomy. The accumulated platelets are activated in the liver sinusoids due to the shear stress leading to release of growth factors like VEGF-A. The solid mechanism is yet to be explored.

質問２）Is there difference in IP VEGF-A expression between HBV and HCV groups?

回答）We didn't find any difference in the concentration of IP VEGF-A between the etiologies : HBV, HCC or non-viral.

質問３）Is there any difference in expression of IP VEGF-A with or without cirrhosis?

回答）We didn't observe difference in IP VEGF-A concentration in HCC patients with or without cirrhosis.

質問４）When does IP VEGF-A increase after PH? Do you have data on time course after PH?

回答）We chose a time point i.e. four weeks after partial hepatectomy to study the late phase of liver regeneration. Thus, we lack the evidence to show its dynamic at different time points.

質問５）How is soluble VEGF receptor (sVEGFR)-1 level regulated?

回答）I apologize, I couldn't find any solid evidence on its regulatory factors.

質問６）Is sVEGFR-1 associated with HCC progression?

回答）To my knowledge, there may not be any robust evidence on it. However, sVEGFR1 is previously shown to regulate VEGF induced angiogenesis and tumor development in murine hepatocellular carcinoma cells.

質問７）The other growth factors/cytokines like EGF, Ang-1, HGF, PDGF, IL-6 and TNF-α moves in sequential manner. Why did you analyze only after four weeks of surgery?

回答）We first planned to assess the change in IP VEGF-A concentration in HCC patients after one month of tumor resection. But opposite to our speculation, we found more increase in IP VEGF-A concentration; this was the point where we started finding the fate of this elevated IP VEGF-A in liver regeneration. So, we missed to collect the intermediate sampling.

質問８）Does the IP VEGF-A concentration peak at four weeks of partial hepatectomy?

回答）We cannot conclude this from our study. One existing study shows that serum VEGF-A level starts to increase one week after partial hepatectomy, however, that study didn't follow on the later days.

質問９）Is it a weak point of your study not comparing IP VEGF-A with direct liver regeneration?

回答）I completely agree, with no intermediate sampling, we missed to provide more direct mechanistic evidences.

質問１０）Should platelets transfusion taken as a measure to improve liver regeneration after partial hepatectomy?

回答）Platelet transfusion and thrombocytosis were shown to enhance hepatocyte proliferation in experimental models. Even in humans, immediate low postoperative platelet count is an independent predictor of liver function after partial hepatectomy. It needs special attention to find if platelet transfusion itself is beneficial to induce liver regeneration after hepatic resection in humans.

質問１１）Do you explain the difference in role of PDGF and IP VEGF-A?

回答） Even if PDGF and VEGF-A are both known as angiogenic growth factors, PDGF is more involved in stromal cells proliferation, while VEGF-A is the most potent growth factor for endothelial cell proliferation known so far. We found rise of platelet VEGF-A but not PDGF-BB at later (angiogenic) phase of liver regeneration.

質問１２） Did you examine the expression of IP VEGF-A in resected liver tissue by protein expression?

回答) We could have obtained better evidences by histological analyses of hepatic parenchyma, describing neo-angiogenesis in association with IP VEGF-A expression. We didn't perform histological analyses in the resected liver tissue in this study, but we will strictly consider it in our further study.

質問１３） Was preoperative level of IP VEGF-A higher in major hepatectomy group? Can you explain the reason?

回答) Though tumor size alone does not determine the extent of resection itself, several cases in major hepatectomy group in this study had relatively bigger tumor size, this might resulted in higher IP VEGF-A preoperatively in major group.

質問１４） Do you have data regarding IP VEGF-A association with clinical outcome and recurrence?

回答） At present, we do not have such data. Since we now have a good time interval to assess recurrence after partial hepatectomy, we are now considering it for our next study.

質問１５） In early phase, growth factor specific for hepatocyte is essential and angiogenesis occur later, is it correct?

回答） Early phase is indicated by proliferation of hepatocytes and later phase is more distinct with vascular remodeling and proliferation of non-parenchymal cells. This could be the reason why HGF concentration is traced higher in early days after hepatectomy. Concrete evidences on the phases of human liver regeneration are yet to be explained.

質問１６） You have shown baseline characters and their association with IP VEGF-A. You should better show the difference of patient characteristic in major and minor group?

回答） We completely agree and consider this useful suggestion. In this study, we wanted to check if these baseline characters affect IP VEGF-A concentration. So, we just performed tests to find if IP VEGF-A is distinctly different in subgroups of an individual trait. It would have been much better analyzing each character in major and minor group.

質問１７） Comparison of IP VEGF-A should be better done between minor pre-op and minor post-op and between major pre-op and major post-op, instead of comparison between minor pre-op and major pre-op or minor post-op and major post-op?

回答） As your suggestion, we also analyzed the difference of IP VEGF-A concentration between the subgroups: IP VEGF-A was significantly elevated in minor post-op compare to minor pre-op; in case of major group, we achieved just a marginal statistical significance even if the median of post-op IP VEGF-A was distinctly higher. This might have been resulted from small patient number in major group.

質問１８） Did you show the actual data of IP VEGF-A association with tumor staging, vascular invasion?

回答） We have presented the association in table, however, we didn't show graphical plotting itself in the paper.

質問１９） You have shown increased serum IL-6 postoperatively, is it associated with IP VEGF-A production?

回答） Previous reports have shown association of IL-6 and IP VEGF-A production in tumor models. Even though there are several regulatory factors, elevated IL-6 might be one of the important factors associated with IP VEGF-A production during liver regeneration as shown by us.

質問２０） Do the same factors stimulate IP VEGF-A in HCC and after partial hepatectomy?

回答） It is very important insight for future investigations, we believe that no evidence exists on this regard.

質問２１） What is the role of sVEGFR-1 in late phase of liver regeneration?

回答） sVEGFR-1 as a neutralizing receptor binds to free VEGF-A and diminishes the actual amount binding to endothelium. As an anti-angiogenic agent, sVEGFR1 suppresses liver sinusoidal endothelial cells proliferation during liver regeneration.

質問２２） What kind of factor stops liver regeneration?

回答） There are many signals or genes known to terminate liver regeneration; among them TGF-β has gained much attention.

質問２３） Is there any factor to stop angiogenic phase of liver regeneration?

回答） Concept of angiogenic phase in liver regeneration is itself a fresh explantation. No studies have shown about its termination.

質問２４） Does Angiopoetin-1 contribute in later phase of liver regeneration?

回答） Angiopoetin-1 level from platelets did not change in the later phase of liver regeneration, may be it is more important in early phase. We could not provide concrete evidence on it.

以上の結果から、５名の審査委員は申請者が大学院博士課程修了者としての学力・識見を有しているものと認め、博士（医学）の学位を与えるに足る資格を有するものと認定した。