Reply to Notch1 and Notch2 have opposite prognostic effects on patients with colorectal cancer

We thank Shigeo Masuda for the interest in our findings and concerns raised. We also appreciate this opportunity to clarify some important issues in our investigation. Shigeo Masuda has questioned antibodies utilized in our investigation. In our previous two reports [1, 2], the main purpose was to evaluate the expression of Notch1 and Notch2 receptors in human colorectal cancer (CRC). As we involved not only western blot and immunohistochemistry but also real-time PCR in the two investigations. We selected Notch antibodies that recognize the inactivated form of Notch receptors for we considered that it could better represent the expression of Notch receptor compared with antibodies that recognize the activated form of Notch. However, we believe the methods to evaluate the activated form of Notch1 receptor by antibody against Val 1744 or Hes-1 suggested by Shigeo Masuda is valuable and practicable. In appropriate circumstances in our future investigation, we will consider them. Since the function of Notch pathway, which could affect the prognosis for CRC patients, is induced by activated Notch receptors, in the present study focused on the prognostic effect of Notch1 and Notch2, the antibodies we selected were Notch intracellular domain antibodies, which are activated Notch antibodies. We also appreciate Shigeo Masuda’s interest in our Kaplan–Meier survival analysis [3]. Despite this, whether the mechanism of Notch pathway activation is ligand dependent or ligand independent and specific ligand in adjacent cells binds to glycosylated or non-glycosylated receptors still need to be further studied. We wish studies on function and mechanism of Notch pathway will eventually contribute to molecular-targeted therapy on human malignancy.

We know that Notch pathway has been proved to play a role in tumor angiogenesis. In our previous report, we aimed to evaluate the expression of Notch receptor in CRC. The thesis of our previous reports considered the malignant biological behaviors of human CRC as integrity and subjected total tissue proteins to western blot analysis. We did not mean to exclude Notch expression in vascular endothelial cells or analyze its expression in vascular endothelial cells separately. Vascular endothelial cells might exist, but it is relatively rare in tissue sections especially in tissue microarray. Our previous reports mainly relied on statistical analysis of staining. Vasculature Notch staining in single tissue section without control can hardly clarify the function of Notch in tumor angiogenesis. We have proved that Notch1 was highly expressed with depth of invasion, especially in T3 and T4 tumors. But the invasion ability of CRC may not be affected dominantly by tumor angiogenesis. Notch pathway can also affect tumor invasion ability by activation of matrix metalloproteinases through nuclear factor-kB pathway, which is known as noncanonical Notch pathway [4–9].

In summary, we sincerely appreciate the helpful comments from Shigeo Masuda on our investigations. We believe that the precise mechanism of activation of Notch pathway and Notch expression in tumor vasculature should be further studied.

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