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

I read with interest the article by Chu and colleagues [1] revealing the prognostic role of Notch1 and Notch2 in colorectal cancer. Their clinical tumor specimens over 1000 are outstanding, and follow-up data of survival are valuable. However, I have several comments and questions regarding this study.

First, it would be interesting to know whether Notch1 or Notch2 expression is a functional marker or just a surrogate marker in predicting prognosis. To address this question, it should be examined whether the activated forms of Notch1 and/or Notch2 proteins were expressed in the specimens. After ligand stimulation, Notch receptors are well known to be processed by proteases, resulting in truncated forms, which are called an activated form. Therefore, in western blotting, a truncated band will be detected in case of active state of Notch receptors. In their previous reports [2, 3], the size of bands in western blotting was unique, and these appeared to be non-truncated bands. These proteins can be confirmed by using an antibody against Val 1744, which is able to recognize the truncated (activated) form of Notch proteins specifically. Alternatively, Hes-1 expression might be useful.

The authors mentioned that the localization of Notch1 and Notch2 was mainly the cytoplasm and cell membrane [2–4], suggesting that Notch1 and Notch2 are inactive. On the other hand, if Notch signaling is activated, next interest is whether the mechanism of activation is ligand-dependent or ligand-independent, or whether a specific ligand in adjacent cells binds to glycosylated or nonglycosylated receptors. Moreover, in that case, molecular-targeted therapy might be promising [5], considering that Kaplan–Meier survival curves in their studies [1, 4] are quite impressive. Second, I think it would be required to recognize Notch1 expression in tumor vasculature, instead of tumor itself. Notch1 and Notch4 are also known to be involved in vascular endothelial cells. However, in their papers [2, 3], total tissue proteins (perhaps including vascular cells) were subjected to western blotting. My concern is that contaminated tumor vascular endothelial cells, in addition to tumor cells, might be evaluated in western blotting. To confirm the results precisely, figures of immunohistochemistry (missed in their studies [1–4]) will give us the definite information on distribution and intensity of Notch1 protein both within tumor itself and within tumor vasculature. Anyway, the authors stated that Notch1 was highly expressed with depth of invasion, especially in T4 and T3, and that depth of invasion is a very important prognostic factor [4]. That is why tumor vasculature with deep infiltrate depth should be separated from tumor itself and carefully evaluated. Taken together, I believe that, through this discussion, this study with large number of clinical samples will be valuable and contribute to future clinical outcome in colorectal cancer treatment.

S. Masuda*
Divison of Regenerative Medicine, Center for Molecular Medicine, Jichi Medical University, Tochigi, Japan
(*E-mail: smasuda-tky@umin.ac.jp)

disclosure
The author declares no conflict of interest.

references

doi:10.1093/annonc/mdr307
Published online 27 June 2011