breast cancer tumorigenesis. Since Jönsson and colleagues have a protocol for isolation of the nuclei of primary breast tumours, perhaps it would be profitable to prepare a nuclear lysate, which could be analysed by Western blotting for the presence of the β-catenin protein. Hopefully, this could definitively answer the question once and for all.

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Response

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In a letter to the Editor published in this issue of the *European Journal of Cancer* pp. 669–670 Rahn and Hugh illuminated the difficulties in detecting β-protein in the nuclei of breast tumour cells. These authors were unable to demonstrate the nuclear localisation of β-catenin in 71 investigated breast tumours (33 invasive ductal, 16 invasive lobular, 21 mixed ductal-lobular, ductal carcinoma *in situ* (DCIS), but they were successful in detecting immunoreactive β-catenin in the nucleus of colon and ovarian carcinomas.

We have previously reported the same difficulties in nuclear staining of β-catenin protein in breast tumour cells, and Rahn and Hugh have recommended that we use an alternative method to circumvent this problem. The method they suggested is based on isolation of the nuclei from primary breast tumour cells and subsequent western blot analysis of the nuclear lysate for presence of β-catenin. This might work well for larger tumours, but it has an obvious shortcoming in that the majority of breast tumours removed from patients are small, therefore isolated nuclei will not provide sufficient protein to allow detection by western blotting. In addition, there is a risk that the nucleic β-catenin protein will be contaminated with cytosolic β-catenin during cell lysis and isolation of nuclei from the cell extract, which would make it impossible to interpret the results.

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It is interesting that Rahn and Hugh failed in their attempts to stain nucleic β-catenin protein in breast tumour cells, whereas they were able to detect this protein in the nuclei of colon tumours when using the same antibody. This suggests that the absence of β-catenin in nuclei of breast tumour cells might not be due to technical problems, but instead reflect the diversity of β-catenin signalling pathway between breast and colon cancer. In support of this idea, several groups have provided evidences that the Wnt/β-catenin signalling pathway in breast cancer does not follow the pattern observed in colon cancer and melanomas [1–3]. In this context, adenomatous polyposis coli (APC) has been recognised as one of the most affected components in the Wnt/β-catenin signalling pathway in colon cancer (80–95%), but not in breast carcinomas (1–5%). Inasmuch as breast and colon epithelial cells are different cell types, and breast cells are influenced by the presence of steriod hormones, the variations in the Wnt/β-catenin signalling pathway indicate that the initiation and promotion of the Wnt/β-catenin signalling in breast cells could be cell-type specific.

The absence of β-catenin in the nucleus of breast cancer cells could also mean that removal of this protein from the nucleus is carried out more effectively by an intact APC protein in breast tumour cells than by a mutated APC in colon tumour cells. In support of this, Henderson has demonstrated that APC protein regulates the subnuclear localisation of β-catenin, that is, he discovered that APC is a nuclear shuttling protein that enters the nucleus and competes with T-cell factor (TCF)/lymphocyte enhancing factor (LEF) for β-cat-

enin binding [4]. Thus, the intact APC protein in breast tumour cells might be able to eliminate nucleic β-catenin protein by binding to it and exporting it from the nucleus to the cytoplasm for degradation.

On the other hand, β-catenin is a multifunctional protein, hence it may be induced in breast cancer cells in response to alterations of other signalling pathways, such as cell cycle progression, cell survival, and as yet unidentified pathways [5]. Because defects in other components participating in Wnt/β-catenin signalling (e.g. conductin, axin and glycogen synthase kinase (GSK)-3β) could lead to the accumulation of cytoplasmic β-catenin, further studies will be needed to reveal the defects that govern the subcellular localisation of β-catenin in breast cancer.

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