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HER2 and proliferation of wound-induced breast carcinoma

Sir—We agree with Elda Tagliabue and colleagues (Aug 16, p 527)[1] that overexpression of HER2 by breast carcinoma cells has a role in their postoperative growth stimulation. However, we believe the interpretation of their results is incomplete, since angiogenesis was not considered as a mechanism of disease.

Results of numerous studies suggest that tumour progression and development of metastases in breast cancer are dependent on angiogenesis, and that *HER2* amplification is closely associated with increased angiogenesis and expression of vascular endothelial growth factor (VEGF).[2] The blocking antibody against HER2, trastuzumab, inhibits VEGF expression and tumour cell growth.[3] Angiogenesis might also play a part in physiological processes, involving tissue repair.[3] VEGF, angiopoietin, fibroblast growth factor, and transforming growth factor β are among the most potent angiogenic cytokines in wound angiogenesis.[4] Finally, the stimulatory effect of trauma on angiogenesis could explain why dormant metastatic tumour cells proliferate after surgery. The signal for this action seems to be the release of angiogenic peptide factors in response to wounding at the primary and secondary surgical insults. Enhanced postoperative angiogenesis and micrometastatic proliferation might also be due to resection of the primary tumour and removal of its inhibitory effect.[5]

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Authors' reply

Sir—Angiogenesis is a key process in the metastatic progression of breast carcinomas, and metastases cannot develop without new vessel formation. However, vascularisation is necessary but not sufficient, since proliferation of tumour cells is also needed. *HER2* is an important oncogene in breast carcinoma pathology, because its signaling pathway increases both proliferation and angiogenesis through induction of VEGF production.[1] After surgery, angiogenesis can be increased directly by endothelial growth factors produced during the healing process and acting on endothelial cells in the vicinity of occult metastatic foci, and indirectly by VEGF released through HER2 activation on tumour cells. Accordingly, we noted that all post-surgical drainage fluids tested stimulated proliferation not only of tumour cells through epithelial growth factors, but also of human umbilical vein endothelial cells through endothelial growth factors. Moreover, induction of proliferation of both cell types by different drainage fluids displayed a similar extent of heterogeneity, suggesting that the degree of endothelial growth factor, like the degree of epithelial growth factor, is related to the extent of surgery as well as to the age of the patient.[2]

The observation that HER2-positive breast carcinomas, unlike their HER2-negative counterparts, show a high peak of early recurrence after surgery[3] raises the possibility that epithelial growth factors that act on HER2-positive tumour cells underlie the stimulation of metastatic growth, since HER2 activation stimulates both proliferation and angiogenesis. Alternatively, as suggested by Mesut Tez, endothelial growth factors directly released from the wound could play the major part, with a higher likelihood of angiogenic stimulation in HER2-positive occult metastatic lesions related, for example, to a higher prevalence of endothelial cells, consistent with a role for HER2 in inducing angiogenesis.[4] Also possible is that the greater likelihood of HER2-positive than HER2-negative tumour cells to exhibit heightened invasiveness and metastatic potential[5] leads to growth stimulation by angiogenesis induction of a greater number of occult metastatic foci present in patients at the time of surgery. In both instances, if angiogenesis induced by endothelial growth factors released during wound healing is the most relevant event for induction of disease recurrence, the use of trastuzumab to block HER2 activity might not be effective in preventing relapses. A clinical trial with perioperative trastuzumab treatment is ongoing to address this issue.

Metastatic growth is a multistep process, but identification of one key event might be sufficient to develop specific therapeutic modalities. Independent of the actual growth factors involved in stimulating breast carcinoma recurrences, surgical intervention limited only to the extent deemed mandatory might help in the control of HER2-positive metastatic spread.

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Sir—Elda Tagliabue and colleagues' report[1] emphasises the complexity of cell-growth regulatory mechanisms involved in breast cancer but, in our