Parallel progression of tumour and metastases

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The Opinion article (Parallel progression of primary tumours and metastases. *Nature Rev. Cancer*. **9**, 302–312 (2009))¹ by Christoph Klein discusses two models of metastasis that differ in their respective roles of adaptation versus selection in the metastatic behaviour of primary tumour cells^{2,3} and in the size at which primary tumours reach for dissemination to occur. Models of metastasis must take into account clinical data regarding tumour size at dissemination. More than 7,000 patients with breast cancer treated in a single institution with the same protocol before the use of adjuvant therapy were studied. The relationship between the incidence of distant metastases at diagnosis and during a follow-up of at least 20 years after initial treatment, and the volume of the tumour (measured on the mastectomy specimen), which is used to determine the volume beyond which cells that initiate metastases cannot leave the tumour, was investigated^{4–6}. The distribution of the tumour volumes was unimodal with a large variance, the occurrence of metastasis was maximal for tumours of ~3 cm in diameter and decreased in larger tumours (FIG. 1a). One-fifth of the disseminations occurred in patients with tumours smaller than 1.5 cm in diameter.

These data are not consistent with the parallel progression model. They are also inconsistent with the linear progression model described by Klein¹. However, they are consistent with the linear progression model when it is assumed that there are two types of cells in tumours: those that can initiate metastases (metastasis-forming cells (MFCs)), which probably derive from tumour stem cells⁷ and those that probably cannot initiate metastasis because their proliferative ability is limited^{7–9}. The presence of tumour stem cells in human tumours is now recognized⁷: they constitute a small minority of tumour cells, which explains why the comparison between cells initiating metastases and tumour cells is not informative.

The decreased probability for tumours larger than 3 cm in diameter to produce metastases might be explained by two hypotheses that are not mutually exclusive. First, the proportion of MFCs during tumour growth decreases and this hypothesis

is consistent with FIG. 1b (based on our published data^{4–6,9,14}). FIG. 1b shows that the probability of metastasis initiation per billion of tumour cells decreases during tumour growth. Second, the biological characteristics of MFCs differ between breast tumours, whereby some cells migrate and seed earlier than others.

In ENT6 mouse tumours, clonogenic cells were identified and it was shown that their cell cycle duration (and therefore their biological characteristics) differed from that of other tumour cells¹⁰. In human breast tumours the presence of stem cells is recognized, but their proportion is very small⁷. These data confirm the existence of two types of tumour cells, which is the main difference between previous models^{8,9} and those discussed by Klein¹. Our model is consistent with clinical studies^{5,6,11,12,14}, which explains the prognostic significance of nodal involvement and histological grade, and the higher risk of dissemination in patients with local recurrence¹³. It provided the basis for screening¹² and predicted that early detection and screening would decrease breast cancer mortality by ~30%^{9,12}, in accordance with data^{14,15}. It also explains the effectiveness of adjuvant therapy.

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doi:10.1038/nrc2627-c1

Figure 1 | Probability of a first distant metastasis initiation according to tumour volume. Based on published data^{4–6,11}. **a** | The proportion of patients for whom the first metastasis initiation occurred during the previous tumour volume doubling. **b** | The probability of a first initiation of a metastasis per 10⁹ cells in the tumour.

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Acknowledgements

The authors acknowledge the clinicians involved in the treatment of breast cancer at Institut Gustave Roussy.

Competing interests statement

The authors declare no competing financial interests.