Cell Biology of Lymphatic Metastasis
The Potential Role of c-erbB Oncogene Signalling

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Abstract

Lymphatic metastases are an important indicator of the malignancy of epithelial cancers. Empirical clinical observations associating specific genetic abnormalities with tumour progression, allied with basic laboratory investigations, are providing not only improved prognostic and diagnostic opportunities, but also a detailed understanding of the molecular machinery of metastasis. One such association – between the c-erbB oncogene family and metastasis – has proved particularly instructive. Functional links between overexpression (and occasionally mutational activation) of c-erbB-1 (EGFR) and c-erbB-2 and specific phenotypes of metastatic cells have been elucidated. Activated c-erbB oncogenes potentiate tumour cell adhesion to endothelial cells and upregulate VEGF, potentially facilitating angiogenesis and vascular invasion. In addition, cells over-expressing these oncogenes frequently show aberrant cell-cell and cell-matrix interactions, mediated by changes in integrin and cadherin function. Thirdly, both EGFR and c-erbB-2 signalling can significantly upregulate specific matrix metalloproteinases, key enzymes involved in angiogenesis and invasion. Finally, c-erbB receptors linked to the actin cytoskeleton and highly expressed on invadopodia, are thought to assist cell migration. Taken together, these observations suggest that such receptors can act as “master switches” in metastasis, whose activation co-ordinately controls events normally utilised in development, now subverted by the metastatic cell. As such, they represent ideal targets for therapeutic intervention.

Introduction

Lymphatic metastases are frequently the first indication of cancer spread and are an extremely important factor in staging and prognosis of many carcinomas. In some cases (e.g., breast cancer) it is possible to sample regional
nodes during surgery to test for the presence of disseminated cells. However, detection depends upon either histological examination of a limited number of sections, which may miss small tumour deposits, or genetic techniques such as PCR or RT-PCR which (at least with some primers) may give false positive results, (Bostick et al. 1998). Recently, attention has turned to molecular profiling of primary tumours in an effort to obtain additional prognostic information. Empirical data have indicated associations between expression of certain molecules in human cancers (for example the c-erbB family of proto-oncogenes) and increased risk of metastasis. These clinical observations, combined with fundamental laboratory research, are now leading to a greater understanding of how such molecules may contribute to key processes involved in tumour dissemination.

The process of metastasis begins with the dissociation of cancer cells from the primary mass, invasion of surrounding tissues and their infiltration into blood vessels and/or lymphatic channels. Frequently (but not inevitably) metastases arise in the first tissue or lymph node encountered, and a cascade of tertiary sites may subsequently be colonised “downstream” of this initial focus or sentinel node. However, interactions between tumour cells and endothelial cells of the vascular and lymphatic channels may significantly affect both the extent and location of metastases. Key factors involved in metastasis have been identified as:

- Angiogenesis: prior to the vascularisation of a small focus of transformed cells, dissemination cannot occur; it is also critical for sustained growth of micrometastases.
- Adhesion: critical alterations in cell-cell and cell-matrix adhesion can promote dissemination and influence sites of attachment and invasion.
- Proteolysis: localised proteolysis assists tumour cell invasion, intravasation, and extravasation and is also required for capillary outgrowth in neoangiogenesis.
- Motility: contributes to tumour cell invasion when coupled to proteolytic activity.

This paper briefly outlines some of the basic mechanisms involved in tumour cell invasion and metastasis, with special reference to the possible role of c-erbB oncogenes in lymphatic dissemination.

**Associations Between c-erbB Oncogene Expression and Metastasis**

We have been interested in the significant associations between over-expression of the c-erbB oncogene family and poor prognosis in a variety of cancers (reviewed in Modjtahedi and Dean 1994, Gullick 1998, Eccles et al. 1995, 1998) and have been exploring the possible molecular bases for these observations. The c-erbB type 1 receptor tyrosine kinase family comprises four known members; epidermal growth factor receptor (EGFR/c-erbB-1) c-erbB-2, c-erbB-3 and c-erbB-4. A large family of ligands can bind to and activate EGFR (EGF, HB-