including the signal transducers and activators of transcription, mitogen-activated protein kinase (MAPK), AKT, and phospholipase C pathways. These pathways mediate various cellular responses, including cell proliferation, survival, cell motility, invasion, and adhesion (Yarden and Sliwkowski 2001). These cellular functions play crucial roles in the process of tumour cell invasion. It is widely accepted that EGFR and its ligands are overexpressed in a number of epithelial tumours (Hynes and Lane 2005). The EGFR ligand, transforming growth factor α, EGFR mRNA, and protein are highly overexpressed in tumour specimens of patients with HNSCC when compared with normal controls (Grandis et al. 1998). HNSCC with nodal involvement have a significantly higher gene copy number of EGFR than HNSCC tumours without nodal involvement (Todd et al. 1989). Elevated levels of another EGFR activating ligand, amphiregulin, have also been implicated in HNSCC. Recombinant amphiregulin can increase the growth, invasive capacity, and migration of oral cancer cells, at least in part, via induction of the inflammatory mediator COX-2 (Tsai et al. 2006)

ROLE OF EGFR SIGNALLING IN INTERCELLULAR ADHESION:

Dissociation of cell–cell adhesion plays an important role in tumour metastasis. Two major mechanisms of cell–cell adhesion are adherence junctions and desmosomes. Adherence junctions are adhesive complexes that utilize cadherin and catenin to bind to microfilament networks within the cell (Perez-Moreno et al. 2003). Desmosomes are adhesive structures that anchor to intracellular intermediate filament networks through the interaction of various adaptors proteins such as desmoplakin, plakoglobin, and cadherin (Yin and Green 2004). Disruption of adherence junctions through the reduced expression of E-cadherin, a-catenin, and b-catenin is associated with regional lymph node metastasis in HNSCC (Tanaka et al. 2003). EGFR signalling pathways play a critical role in the regulation of these adhesive complexes. Thus, the interplay between EGFR signalling and intercellular adhesion is probably a major component of tumour metastasis and cancer progression. E-cadherin has proven to be an important molecule in the progression of cancer and can serve as an indicator of the metastatic potential of a primary tumour. Expression of E-cadherin negatively correlates with histologic grade, tumour size, clinical staging, lymph node metastasis, and tumour invasion and correlates with a poor prognosis in oesophageal SCC (Zhao et al. 2003). Loss of E-cadherin expression in the primary tumour correlates with development of nodal metastasis, tumour progression, and poor prognosis for patients with HNSCC (Bankfalvi et al. 2002; Lee et al. 2002). In three-dimensional organotypic models, suppression of E-cadherin leads to a more invasive phenotype of squamous cell carcinoma cell lines, whereas maintenance of E-cadherin expression can prevent invasion both in vitro and in vivo (Margulis et al. 2005). EGFR and its ligands have been shown to be the key regulators of E-cadherin expression. EGFR modulation of E-cadherin is not only important for tumour metastasis but also is involved in the epithelial-to-mesenchymal transition (EMT). A common downstream target of EGFR is the phosphoinositide 3 kinase (PI3K)/Akt pathway. Phosphorylated Akt has been shown to be inversely correlated with E-cadherin expression in HNSCC (Lim et al. 2005). Akt activation represses E-cadherin expression through upregulation of the repressors SNAIL and SIP1 (Grille et al. 2003). Thus, it can be postulated that EGFR overexpression leads to increased activation of the PI3K-Akt pathway resulting in upregulation of the E-cadherin SNAIL and SIP1 (see Fig. 9.2).

Furthermore, E-cadherin is likely endocytosed through the EGFR/caveolin-1 dependent pathway leading to cell–cell detachment and increased invasive capacity. Desmosomes are important structures involved in cell–cell adhesion as well as intracellular signalling. There is accumulating evidence implicating desmosomes in the progression of cancer. A number of cancers have shown