On Mammary Gland Growth Factors: Roles in Normal Development and in Cancer

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Extensive studies on mammary gland growth factors have shed light on their roles in normal mammary development and cancer, as described nicely by Hynes and Watson (2011). Here I would like to highlight some novel emerging areas of the field. Aside from their essential roles in normal breast development, receptor-tyrosine kinases (RTKs) have been found to be highly expressed and activated in human cancers, which is frequently associated with poor prognosis. Both monoclonal antibodies and tyrosine kinase inhibitors (TKIs) targeting epidermal growth factor receptor (EGFR) and ErbB-2 have been developed as effective targeted anti-cancer therapies, and many have been approved by the FDA such as cetuximab, trastuzumab, lapatinib, and gefitinib. Moreover, emerging evidence is revealing novel aspects of RTK function, such as posttranslational modifications, cell surface to nucleus trafficking, and kinase-independent activities.

Posttranslational modifications of RTKs such as phosphorylation and ubiquitination play important roles in RTK activation and degradation. Recently, another modification, acetylation of EGFR was identified on three lysine residues in the EGFR carboxy-terminal domain and could regulate EGFR internalization and the downstream AKT pathway (Goh et al. 2010). Similarly, histone deacetylase 6 (HDAC6), a cytoplasmic lysine deacetylase, has been found to negatively regulate EGFR endocytosis and deg-

radation (Deribe et al. 2009; Gao et al. 2010). These findings suggest that acetylation/deacetylation regulates EGFR functions. Furthermore, another recent study showed that vascular endothelial growth factor receptor 1 (VEGFR1) can be methylated by SMYD3, a histone methyltransferase (Kunizaki et al. 2007). The studies thus implicate posttranslational modification by acetylation and methylation as regulatory mechanisms for RTKs, but how these modifications might engage in crosstalk with others, such as phosphorylation and ubiquitination, needs further investigation.

Alteration of RTK localization and compartmentalization is associated with several types of cancer, including breast cancer. Expanding our knowledge of subcellular trafficking of proteins such as EGFR-family RTKs is therefore worthwhile. Internalized EGFR is transported to the lysosomes for degradation or recycled back to the cell surface. However, emerging evidence suggests after endocytosis it can also be transported to other cellular compartments. For example, EGFR can shuttle between endosomes and biosynthetic/secretory compartments such as the endoplasmic reticulum and the Golgi apparatus; this retrograde transport (Wang et al. 2010a) is important for diverse cellular functions. In addition, full-length EGFR has also been found in mitochondria and may contribute to cell survival (Demory et al. 2009). A recent report also showed that EGFR and EGFRvIII, a

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constitutively activated EGFR variant, bind to a proapoptotic protein in mitochondria and lead to drug resistance in glioblastoma (Zhu et al. 2010).

Further evidence from several groups indicates the existence of a novel EGFR signaling pathway in which the EGFR-family receptors can be shuttled from the cell surface to the nucleus (Massie and Mills 2006; Carpenter and Liao 2009; Wang and Hung 2009), where they are involved in a variety of cellular functions such as transcriptional regulation, cell proliferation, DNA repair, and chemo- and radioresistance (Wang et al. 2006; de la Iglesia et al. 2008; Dittmann et al. 2010; Huo et al. 2010). Moreover, nuclear EGFR contributes to resistance to the anti-EGFR antibody cetuximab (Li et al. 2009), and a Src inhibitor has been shown to block cetuximab- and radiation-induced nuclear translocation of EGFR (Li et al. 2010). This implicates nuclear EGFR in responses to EGFR-targeting drugs. Nuclear EGFR is associated with poor clinical outcome in multiple cancer types, including breast and ovarian cancers, and oropharyngeal and esophageal squamous cell carcinomas (Lo et al. 2005; Psyrri et al. 2005, 2008; Hoshino et al. 2007; Xia et al. 2009; Hadzisejdic et al. 2010; Wang et al. 2010b).

Despite RTKs being most well known for their tyrosine kinase activities, EGFR has been reported to stabilize a glucose transporter (SGLT-1) to promote glucose uptake in cancer cells independent of its kinase activity (Weihua et al. 2008). The kinase-independent activity of RTKs may help explain the Warburg effect, in which cancer cells use glucose more efficiently than do normal cells, as well as puzzling differential responses to monoclonal antibodies and TKIs in clinical trials. For instance, phase III trials of erlotinib (a TKI) plus chemotherapy failed to improve overall survival in non-small-cell lung cancer (NSCLC) (Herbst et al. 2005), whereas cetuximab plus chemotherapy extended survival for advanced lung cancer (Pirker 2008). It is possible that other RTKs also regulate different glucose transporters.

Although these new functions of RTKs have not been extensively characterized and have often been overlooked, many interesting ques-

tions regarding their roles in mammary gland development and cancer remain to be addressed.

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