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$P2Y_2$ receptors Transactivate the EGFR/ERB1 and ERB3 Growth Factor Receptors in Human Salivary Gland Cells

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The epidermal growth factor receptor (EGFR/ERB1) plays a key role in the regulation of epithelial cell development, differentiation and in the pathophysiology of hyperproliferative diseases such as cancer. Transactivation of the EGFR/ERB1 by G-protein coupled receptors has been shown to be dependent on proteolytic cleavage of membrane ligands such as heparin binding epidermal growth factor (HBEGF), EGF, transforming growth factor α (TGF-α), epiregulin, amphiregulin and betacellulin. Utilizing the human submandibular gland (HSG) cell line, we found that activation of the $P2Y_2$ nucleotide receptor ($P2Y_2R$) by its agonist UTP caused a time-dependent activation of EGFR/ERB1; however, neutralizing antibodies to the known ligands to EGFR/ERB1 failed to inhibit the UTP-induced phosphorylation of EGFR/ERB1. EGFR/ERB1 phosphorylation can also be induced by heterodimerization with one of the other ERB family members, ERB2, ERB3, and ERB4. HSG cells express ERB2 and ERB3 but not ERB4. Since ERB2 is a ligandless receptor, ERB3 is the likely dimerizing partner. Our results indicate that $P2Y_2R$ activation by UTP phosphorylates ERB3. Heregulin, the only known ligand for ERB3 is expressed in HSGs. Therefore, our results suggest that $P2Y_2R$ activation stimulates the formation of ERB3-EGFR/ERB1 heterodimers by cleavage of heregulin and its binding to ERB3.