CASE STUDY: EGF Receptor Signaling and Cancer

The EGF receptor (epidermal growth factor) is a family of cellular receptors that normally responds to differentiation factors, such as EGF. The EGFR is a receptor tyrosine kinase that elicits a signal transduction cascade by first binding to EGF, which induces receptor dimerization and subsequent signaling through the ras MAP kinase pathway. EGFR signaling has been associated with multiple types of cancer. For example, the ErbB oncogene is a defective form of the EGF receptor in which the extracellular EGF binding sites are deleted. While one may initially think that the ErbB protein should be defective in EGFR signaling, ErbB is constitutively active—meaning that it is constantly sending its proliferative signal. In a second example, a single mutation in the extracellular binding domain of the Her2 receptor causes dimerization of the receptor in the absence of EGF. Finally, EGFR overexpression has been associated with certain cancers. Increased expression can be correlated with increased receptor signaling.

Questions:

1. Would increased levels of EGF have an impact on ErbB signaling? Why or why not?

   Answer: No it would not. Because the ErbB receptor has a deletion in the EGF binding site, any additional EGF would not be able to bind to the ErbB receptor and therefore would not increase receptor signaling.

2. Two different classes of inhibitors have been developed to EGFR for clinical use in the treatment of cancer. The first class of inhibitors includes antibodies that bind to the extracellular domain of the EGFR. The second class of inhibitors includes small molecules that can enter cells and bind to the intracellular kinase domain. Why would each of these be effective inhibitors?

   Answer: Antibodies are fairly large molecules so their binding to the extracellular domain is likely to inhibit the binding of the normal EGF ligand thereby preventing receptor signaling. The antibody inhibitors are likely to be most effective on tumors that overexpress EGFR as their effects on constitutively active receptors is likely to be quite small.

   The small molecule inhibitors would inhibit tyrosine kinase phosphorylation, which is needed for receptor signaling. The small molecule inhibitors should be equally effective on cancers that overexpress EGFR as well as those with mutant forms of the EGF receptor that are constitutively signaling.

Where can I learn more?