Alzheimer's drug may prevent breast cancer recurrence

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Current research shows the unregulated growth in cancer cells in breast cancer is linked to the dysfunctional Notch Signaling Pathway. The intercellular domain (Notch-IC) of one of the proteins in this pathway is cleaved in response to binding of the extracellular ligand. In cancer cells, it is present in high levels, and activates a transcription factor responsible for regulating cell cycle genes. DAPT, an Alzheimer's drug has the potential to block extracellular ligand binding, but has some social and medical implications.

Breast cancer is responsible for the deaths of 502,000 individuals a year worldwide, and is the leading cause of cancer deaths among women (Cancer Fact Sheet, 2006). There are many factors leading to the disease, including non-inherited, and inherited genetic mutations, and a variety of environmental elements. The different types of breast cancer begin with the growth of a tumour presenting with the possibility of metastasis. Due to the disease's high incidence, it is important to have an understanding of the current and future therapies available for treatment (About Breast Cancer, 2006).

Treatment Methods

There are several methods currently used to treat breast cancer and prevent relapse. The two major categories of treatments can be seperated into local and systemic; the former targets the immediate area where the treatment is administered, while the latter takes effect in the various systems of the body. Examples of local treatments are surgery and radiation therapy, while systemic treatments include HER-2 therapy, chemotherapy, and hormone therapy. Although these techniques are effective, each are associated with a set of limitations and side effects. For example, treatment via surgery may neglect cancerous cells that have metastasized to other parts of the body, while hormone therapy is a viable treatment only for patients that have cancer growth promoted by the presence of estrogen (About Breast Cancer, 2006). Hormone therapy can also result in side effects such as hot flashes, and if a patient's treatment involves pharmaceutical aromatase inhibitors, osteoporosis can be promoted (Hormone Therapy Side Effects, 2006). In chemotherapy, the development of side effects is specific to the class of drug administered; for instance, taxol induces disorder in the peripheral nervous system (Peilter & Russel, 2006).

Adding to the limited efficacy of the treatments is the risk of relapse confronting the patient once the therapy has concluded. It is for these reasons that funds and resources are diverted into developing novel and effective ways of treating breast cancer and preventing recurrence.

Experimentation with a drug commonly used to treat Alzheimer's disease show promise in minimizing the risk of recurrance in breast cancer patients. The drug is classified as a γ-secretase inhibitor, and works by"attacking" the Notch gene (New Breast Cancer Drug, 2007).

The Notch Gene

The Notch gene was first discovered in Drosophila by Thomas Hunt Morgan in 1917, and has since been identified in humans. The product of the Notch gene is a transmembrane protein that, in mammals, occurs in

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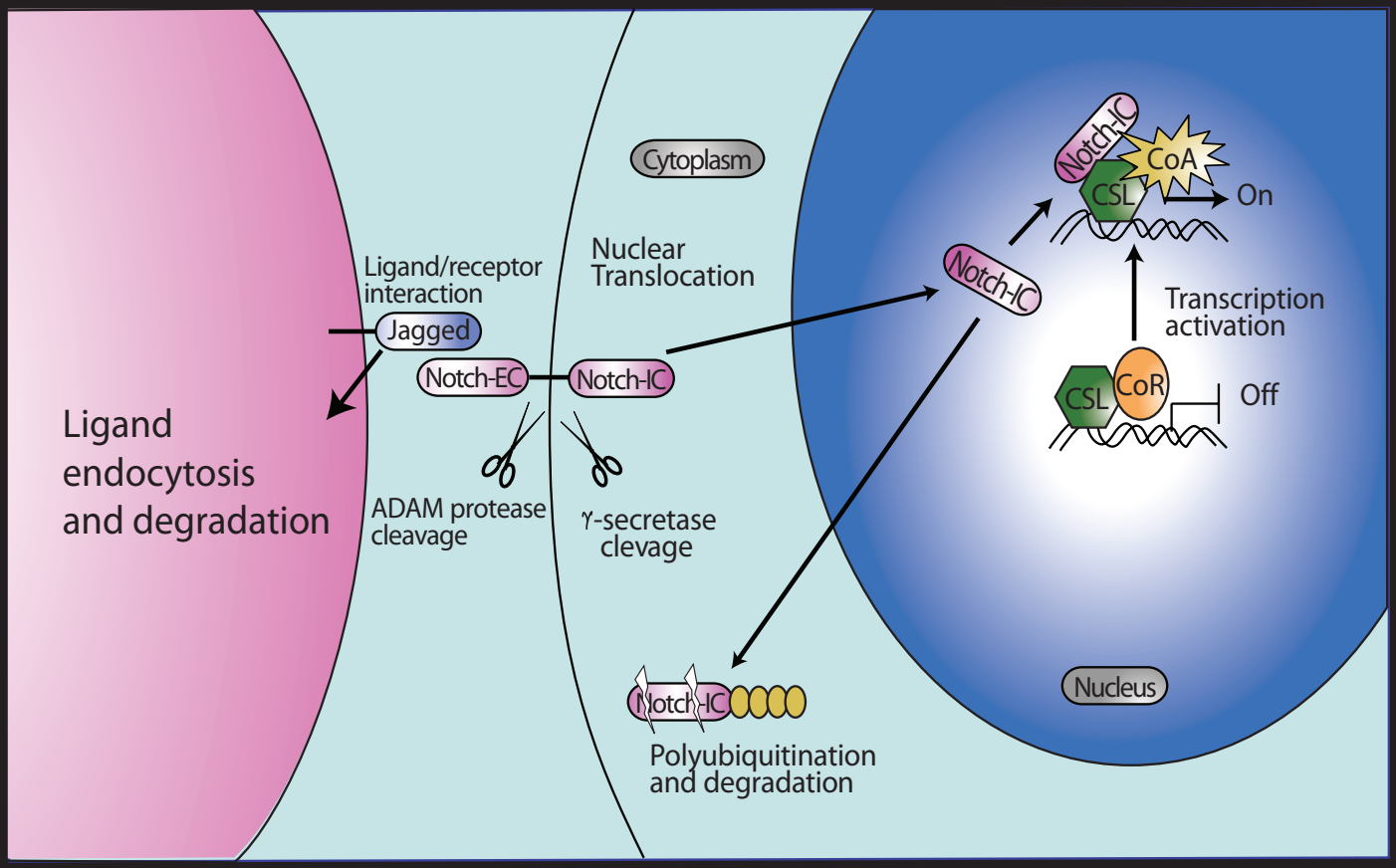

Figure 1 Notch ligand binding and γ-secretase cleavage, leading to the Notch-IC pathway (Shih & Wang, 2007).

four different forms (Notch 1, 2, 3, 4). Each form consists of the same general three-part structure: an extracellular, a transmembrane, and an intracellular components (Figure 1). When expressed physiologically, the protein initiates a signaling pathway within the cell (Harris & Shi, 2006).

Notch Signalling Pathway

The Notch signaling pathway begins with the extracellular domain of the protein, Notch-EC (extracellular), acting as a receptor site for incoming ligands. When a Notch ligand binds onto the Notch-EC structure, γ-secretase cleaves the intracellular domain of the protein, Notch-IC (intracellular), sending it towards the nucleus (Figure 1). A closer look at this mechanism is displayed in Figure 2. Once inside the nucleus, Notch-IC binds to a transcriptional factor called CBF-1. This event results in another protein, Lag-1/CSL, switching from a transcriptional repressor to an activator. The activated protein then transcribes certain genes that have several purposes (Figure 1) (Shih & Wang, 2007).

These products are responsible for the differentiation and maintenance of stem cells in both normal and cancerous development. In terms of the Notch pathway, cancerous cells exhibit high levels of Notch-IC. Recent studies that utilized mouse models and human cells have shown that high levels of the intracellular protein results in the generation of mammary gland tumors (Shih & Wang, 2007).

Gamma-Secretase & Gamma-Secretase Inhibitors

As previously mentioned, γ-secretase is a crucial mediator in the Notch signaling pathway; it allows the Notch-IC in cancerous cells to travel to the nucleus, leading to oncogenic development in the breast. Dr. Robert Clarke and his team of researchers from the University of Manchester showed that using an enzyme inhibitor may be a strategy to prevent the further development of cancer cells.

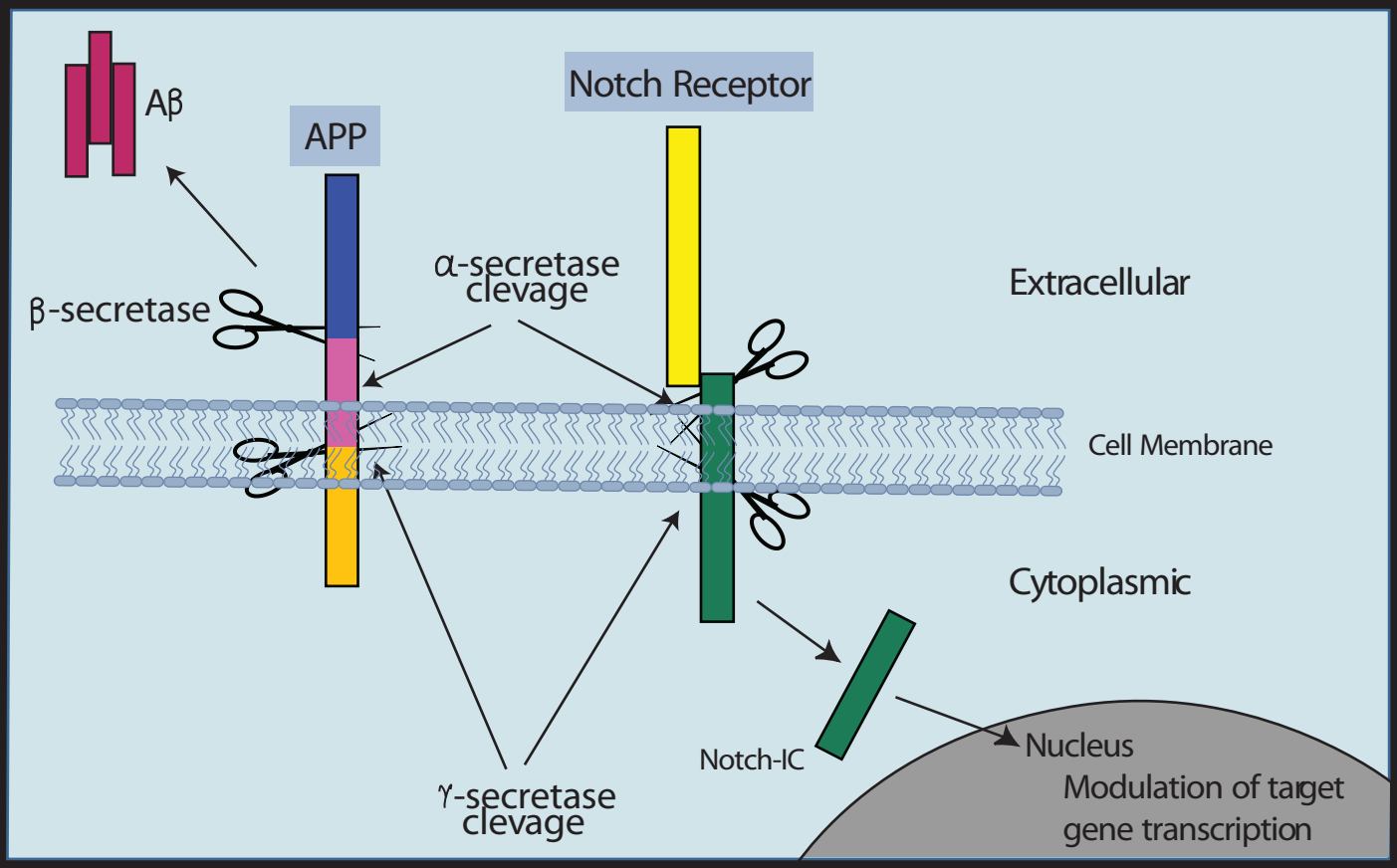

Figure 2 A closer look at gamma secretase cleavage, freeing Notch-IC (Shih & Wang, 2007).

N-[N-(3,5-difluorophenacetyl)-L-alanyl]-Sphenylglycine t-butyl ester, also known as DAPT, in Alzheimer's treatment was used by Clarke et al. in this study (Figure 3). This molecule may have been specifically chosen for its unique ability to inhibit each of the four Notch receptors in humans. The group found that the drug successfully inhibited the intracellular Notch pathway, and thus concluded that DAPT may prevent the recurrence of breast cancer (Clarke et al., 2007).

The remaining obstacles that DAPT must overcome in order to be used in medical practice are its clinical trials. Elucidating the interaction between the drug and normal cells is expected to pose issues for the experimental trials; regular Notch activity is required for normal organ function in certain parts of the body. For example, the Notch pathway contributes to the development of cellular components in the blood. Inhibition of the Notch pathway inhibits the differentiation of stem cells into these blood cells, which can result in organ dysfunction. Another potential drawback of DAPT is that the inhibitor may interact with γ-secretase as well as other molecules not involved with Notch signaling, thus harming regular cell activities. Essentially, the core issue that needs to be addressed is developing target specificity for the drug. However, its trial processes may proceed relatively fast, as its use as an Alzheimer's drug can accelerate the clinical trial process (Shih & Wang, 2007).

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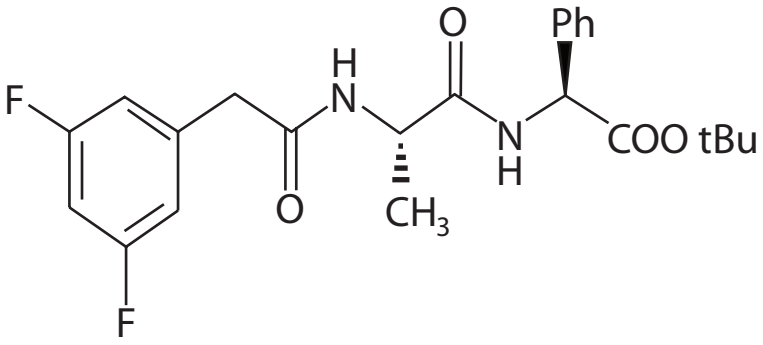

Figure 3 Structure of the DAPT molecule (New Product Highlights, 2004).

Conclusion

Understanding the pathway of the Notch gene in breast cancer, along with the discovery of DAPT's anti-tumour role, has presented scientists with a new therapeutic strategy that can be used to fight cancer. Furthermore, irregular Notch activity has not only been found in breast cancer; research suggests it may be linked to cancer in the lungs, skin, prostate, brain and among other locations. As a result, research involving the Notch pathway and γ-secretase inhibitors such as DAPT is currently at the forefront of oncology (Shih & Wang, 2007).

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