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Introduction

Intensive research over the last three decades has uncovered major mechanisms that regulate the transformation of a normal tissue to a malignant tumor. However, to the disappointment of many molecular biologists, these significant advances in identifying oncogenes, tumor-suppressors, and critical signaling pathways have generated only limited impact in clinical oncology. This frustration may not persist for long: tailor-made drugs developed specifically to recognize molecular targets, and intercept biochemical engines whose intricacy is well understood, are on the verge of revolutionizing contemporary medicine. This issue of *Breast Disease* exemplifies the evolution of an oncogene-encoded enzyme from its discovery to the stage of a fully recognized target for breast cancer therapy.

The rodent neu oncogene was first detected in 1984 by Robert A. Weinberg of the Whitehead Institute. The discovery was made possible because a carcinogen-induced mutation was responsible for dramatic activation of the oncogenic potential of neu. Independently, the groups of Axel Ullrich and Stuart Aaronson, working at the time at Genetech and at the National Cancer Institute, have isolated the same gene. They termed it HER2 and ErbB-2, respectively, because its structure resembled that of the human epidermal growth factor receptor (by itself a homologue of the avian viral ErbB oncoprotein). Interestingly, the oncogenic mutation that turned c-neu into an oncogene was mapped to the transmembrane domain of the receptor tyrosine kinase encoded by neu, but no similar mutations have been identified thus far in humans. Nevertheless, overexpression of the HER2/ErbB-2 protein, primarily as a result of gene amplification, was noted by Denis Slamon and several other investigators in 1987. Since then, numerous studies have linked HER2 with poor prognosis of breast and other types of cancer. Parallel, therapeutic experiments in animal models have suggested that reducing HER2/ErbB-2 expression at the cell surface may be clinically beneficial. One of these approaches recently has matured with the approval of an antibody to HER2 (Herceptin®/Trastuzumab) for treatment of breast cancer patients with a metastatic disease.

The selection of chapters for this issue is aimed at highlighting the intimate associations between basic and clinical research, which is essential for rational drug development. The chapter by Christopher Lacenere and Paul Sternberg reviews the wealth of data accumulated on the evolutionary origin of HER2. Apparently, the ancestral version of the molecule already existed one billion years ago, in the nematode *C. elegans*. Remarkably, not only the structure but also the biochemical mode of action and the physiological function of this receptor tyrosine kinase have been well conserved throughout evolution: by receiving intercellular cues, in the form of growth factors, the invertebrate receptor translates cell-to-cell signals into a genetic program leading to morphogenesis. Development of the lobuloalveolar organ of the mammary gland in mammals is but one example of the evolutionarily conserved role of HER2. No less important is the observation that in both nematodes and humans, HER2 funnels extracellular signals to a linear biochemical cascade, called the Ras-MAPK pathway. Signal transduction events elicited by stimulating HER2 are described by Axel Ullrich and his colleagues. This topical field holds the promise of identifying critical biochemical reactions whose inhibition will abrogate the oncogenic action of HER2.

From a biochemical point of view, HER2 presents an enigma: although it belongs to a family that includes three receptors for many well characterized growth factors, HER2 binds no known ligand molecule. Recent studies, which are summarized by Iris Alroy and Yosef Yarden, offer a solution to the enigma of HER2. Accordingly, HER2 acts as an ancillary protein (co-receptor) to the other three

ErbBs. Therefore, overexpression of HER2 can augment binding of many EGF-like growth factors and consequently can sensitize tumor cells to stromal signals. The realization that HER2 acts in the framework of a signaling network rather than as a solitary receptor identifies the partners of HER2, namely ErbB-1, -3 and -4, as well as their many ligands, as potential targets for drug intervention. Evidently, the site of oncogenic action of the network is the plasma membrane and treatments that remove HER2 from this location can interfere with its action. An example is the natural antibiotic geldanamycin, which leads to rapid degradation HER2, probably by dissociating it from a chaperone that stabilizes HER2 at the cell surface. The clinical potential of geldanamycin and similar small molecular weight antagonists, along with the underlying biochemistry, is reviewed by Len Neckers.

It is important to note that many independent lines of basic research have attributed a causative role to HER2 overexpression in the generation of a relatively aggressive cancer phenotype. Moreover, the oncogenic role of HER2 is non-autonomous, since it cooperates with growth factors and their direct receptors. For these reasons, HER2 presence at high copy numbers may predict disease behavior and response to therapy. On the other hand, inactivation of HER2 may directly influence the course of disease. Sarah Bacus and her collaborators survey the prognostic correlates of HER2 with an emphasis on breast cancer. The importance of HER2 as a predictor of response to chemotherapy and hormonal therapy is covered by Soonmyung Paik and Edison Liu. Their critical review analyzes clinical data regarding systemic therapy of breast cancer and highlights an interesting interaction between HER2 and doxorubicin.

The therapeutic potential of monoclonal antibodies to HER2 was first recognized in 1985, following a report by Mark Greene and his colleagues on an inhibitory effect of anti-Neu antibodies toward rodent tumors driven by the neu oncogene. It has taken thirteen more years and numerous confirmatory studies before the first antibody has been approved for clinical use in the U.S. and other countries. The development of this antibody by Genentech Inc. is reviewed by some of the scientists involved, including Paul Carter and Mark Sliwkowski. These authors detail the considerations they undertook when selecting a specific monoclonal antibody and tailoring it for clinical use. It is anticipated that the experience gained with the growing number of Herceptin®-treated patients will yield important lessons relevant to the application of cancer immunotherapy in general. Furthermore, the successful use of naked monoclonal antibodies may well emerge as the tip of an iceberg of future antibody-based therapies. One example, which is reviewed by Martin Brechbiel and Thomas Waldman, involves the use of antibodies linked to radionuclides. The superior efficacy of radioactive antibodies and techniques that may improve their access to HER2-overexpressing tumors hold promise for the future. Yet, more antibody-based therapeutics are currently in preclinical or initial clinical testing. These technologies, which include enzyme prodrug therapy and immunoliposomes as vehicles for targeted drug delivery, are described by Christopher Benz and his colleagues.

While the cell surface location of HER2 offers significant advantages for therapeutic intervention using extracellularily applied antibodies, several other unique attributes make HER2 an attractive target for alternative strategies. One of these is the development of specific inhibitors of the tyrosine kinase activity of HER2. In the absence of this enzymatic function, the oncogenic action of HER2 is completely disabled. Moreover, *in vitro* studies favor the possibility of selective inhibition of HER2 without affecting the kinases of related receptors. This potential pharmacological strategy is described by Alexander Levitzki and Aviv Gazit. The promoter of the HER2 gene offers yet another target for therapy, for overexpression entails enhanced transcription. In their review, Mien-Chie Hung and Shao-Chun Wang discuss the potential involvement of several transcriptional regulators (e.g., the adenovirus type 5 E1A, the SV40 large T antigen, and the *ets* family member PEA3) and their use in gene therapy targeted at HER2.

Being the first oncogene whose protein product has been targeted by therapy, HER2 offers a glimpse of the future of molecular medicine. If realized, the powerful potential of molecular biology will open new dimensions for targeted therapy of breast and other diseases. Examples not only include vectors to deliver antisense reagents and ribozymes to block HER2 expression but also the use of combinatorial chemistry to generate antagonists of ligands upstream of HER2, as well as inhibitors of enzymes lying downstream of the oncoprotein.

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