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Cyclooxygenase-2 Is Overexpressed in HER-2/neu-positive Breast Cancer

EVIDENCE FOR INVOLVEMENT OF AP-1 AND PEA3*

Kotha Subbaramaiah‡, Larry Norton§, William Gerald¶, and Andrew J. Dannenberg‡‖

From the ‡ Department of Medicine, New York Presbyterian Hospital, Weill Medical College of Cornell University and Strang Cancer Prevention Center and the § Breast Cancer Medicine Service and the ¶ Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York 10021

Markedly increased levels of cyclooxygenase-2 (COX-2) mRNA, protein, and prostaglandin E_2 synthesis were detected in HER-2/neu-transformed human mammary epithelial cells (184B5/HER) compared with its nontransformed partner cell line (184B5). HER-2/neu stimulated *COX-2* transcription via the Ras → Raf → MAPK pathway. The inductive effects of HER-2/neu were mediated, in part, by enhanced binding of AP-1 (c-Jun, c-Fos, and ATF-2) to the cyclic AMP-response element (−59/−53) of the *COX-2* promoter. The potential contribution of the transcription factor PEA3 was also investigated. Elevated levels of PEA3 were detected in 184B5/HER cells. A PEA3 site (−75/−72) was identified juxtaposed to the cyclic AMP-response element. HER-2/neu-mediated activation of the *COX-2* promoter was blocked by mutagenizing the PEA3 site or overexpressing antisense to PEA3. To determine whether HER-2/neu status was also a determinant of COX-2 expression *in vivo*, we compared levels of COX-2 protein in HER-2/neu-positive and -negative human breast cancers. Increased amounts of COX-2 were detected in HER-2/neu-positive tumors. Taken together, these results suggest that closely spaced PEA3 and cyclic AMP-response elements are required for HER-2/neu-mediated induction of *COX-2* transcription. The clear relationship between HER-

2/neu status and COX-2 expression in human breast tumors suggests that this mechanism is likely to be operative *in vivo*.

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‖To whom correspondence should be addressed: New York Presbyterian Hospital-Cornell Campus, 525 East 68th St., Rm. F-206, New York, NY 10021. Tel.: 212-746-4403; Fax: 212-746-4885; E-mail: ajdannen@med.cornell.edu.