The achilles heel of ErbB-2/HER2: regulation by the Hsp90 chaperone machine and potential for pharmacological intervention

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Abstract:

Signal transduction mediated by ErbB/HER receptor tyrosine kinases is crucial for the development and maintenance of epithelial tissues, and aberrant signaling is frequently associated with malignancies of epithelial origin. This review focuses on the roles played by the Hsp90 chaperone machinery in the regulation of signaling through the ErbB/HER network, and discusses potential therapeutic strategies that disrupt chaperone functions. Hsp90 and its associated cochaperones regulate ErbB signal transduction through multiple mechanisms. The chaperone system controls the stability of the nascent forms of both ErbB-1 (EGF-receptor) and ErbB-2/HER2, while regulation of the mature form is restricted to ErbB-2. Regulation by the Hsp90 complex extends to downstream effectors of ErbB signaling, namely Raf-1, Pdk-1 and Akt/PKB. Disrupting the function of Hsp90 results in the degradation of both the receptors and their effectors, thereby inhibiting tumor cell growth. The importance of an Hsp90-recognition motif located within the kinase domain of ErbB-2 is discussed, as well as a direct role for Hsp90 in regulating tyrosine kinase activity. In light of recent observations, we emphasize the ability of specific tyrosine kinase inhibitors to selectively target ErbB-2 to the chaperone-mediated degradation pathway. ErbB-specific drugs are already used to treat cancers, and clinical trials are underway for additional compounds that intercept ErbB signaling, including drugs that target Hsp90. Hence, the dependence of ErbB-2 upon Hsp90 reveals an Achilles heel, which opens a window of opportunity for combating cancers driven by the ErbB/HER signaling network.

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