Despite extensive investigative studies and clinical trials over the past two decades, we still do not understand why cancer cells are more sensitive to the cellular toxicity of Hsp90 inhibitors than normal cells. We still do not understand why only some cancer cells are sensitive to the Hsp90 inhibitors. Based on studies of the past few years, we argue that the selected sensitivity of cancer cells to Hsp90 inhibitors, such as 17-N-allylamino-17-demethoxygeldanamycin, is due to inhibition of the extracellular Hsp90 (eHsp90) rather than intracellular Hsp90 by these inhibitors. Because not all tumor cells utilize eHsp90 for motility, invasion and metastasis, only the group of "eHsp90-dependent" cancer cells is sensitive to Hsp90 inhibitors. If these notions prove to be true, pharmaceutical agents that selectively target eHsp90 should be more effective on tumor cells and less toxic on normal cells than current inhibitors that nondiscriminatively target both extracellular and intracellular Hsp90.
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