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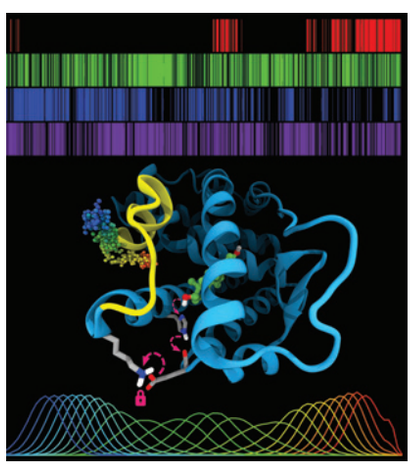
ABOUT THE COVER

Estrogen receptor alpha (ERα) is a ligand-activated transcription factor that is therapeutically targetable with endocrine therapies in approximately 70% of breast cancers. Ligand binding initiates an extended hydrogen bonding network (pink arrows) terminating in an ionic lock that allows helix 12 (H12; yellow) to fold into the active conformation capable of binding coactivating proteins that initiate transcriptional cascades. In their study on page 1559, Mayne and colleagues perform free energy calculations of clinically relevant mutations in the helix 11-12 loop of ERα to determine their effect on H12 conformation and receptor activation. The colored balls and associated histograms characterize the dynamics of the loop preceding H12. Each of the point mutations changes the energy landscape of ERα in a manner that no longer requires ligand binding to form the ionic lock and adopt the active conformation, thereby driving therapy resistance and metastatic disease.



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