Targeting tumors with SHH/M2 smoothened mutation with ER stress inducing molecules

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Technology description

The Hedgehog signaling pathway, an essential regulator of developmental patterning, is implicated as playing causative and survival roles in a range of human cancers. The signal transducing component of the pathway, Smoothened, has revealed itself to be an efficacious therapeutic target in combating oncogenic signaling. However, therapeutic challenges remain in cases where tumors acquire resistance to Smoothened antagonists, and also in cases where signaling is driven by active Smoothened mutants that exhibit reduced sensitivity to these compounds. We previously demonstrated that active Smoothened mutants are subjected to prolonged ER (endoplasmic reticulum) retention, likely due to their mutations triggering conformation shifts that are detected by ER quality control. Researchers at St. Jude have conceived of a way to exploit this biology by using compounds that induce ER stress, such as thapsigargin, to trigger the Unfolded Protein Response (UPR) and target active Smoothened mutants for degradation. This results in attenuation of inappropriate Hedgehog pathway activity and provides an alternative approach to treating these tumors.

Keywords Hedgehog, endoplasmic reticulum, smoothened；

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