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# Baicalein Reverses CAFs Activation in Triple-Negative Breast Cancer by Inhibiting the PI3K/Akt/mTOR Pathway

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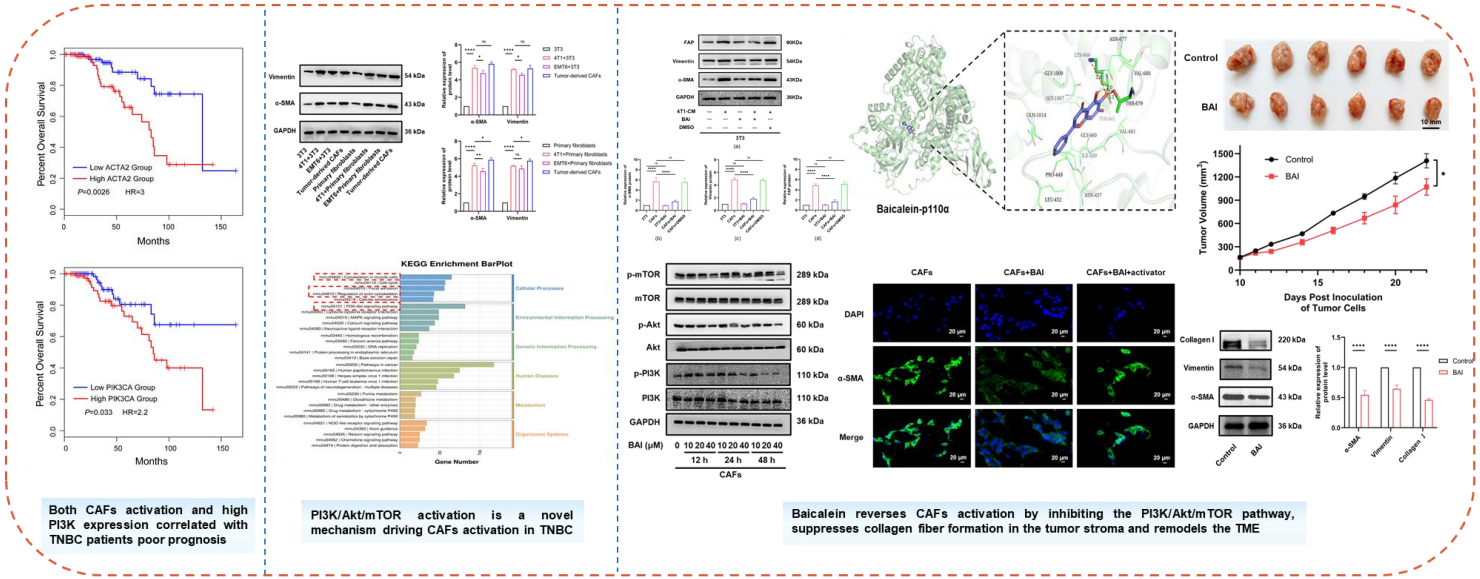
## 01 Background and purpose

Triple-negative breast cancer (TNBC) is the most aggressive subtype with high metastatic potential and the poorest prognosis. Cancer-associated fibroblasts (CAFs) promote tumor progression and treatment resistance. Baicalein (BAI), the primary active constituent of the traditional Chinese herb Scutellaria baicalensis, exhibits broad-spectrum antitumor activity and multi-target effects. Studies on baicalein-mediated regulation of CAFs remain limited, so this study aims to analyze the correlation between tumor-stroma ratio (TSR), CAFs activation markers, clinicopathological features, and prognosis in TNBC; explore novel mechanisms and key molecules underlying CAFs activation; elucidate the role and molecular mechanism of baicalein in reversing CAFs activation, thereby providing a scientific foundation for developing novel TNBC combination therapies.

## 02 Methods

Clinicopathological data from TNBC patients and the TCGA database were analyzed to evaluate the association of TSR and CAFs activation markers with clinicopathological characteristics and prognosis. An ex vivo CAFs activation model was established to investigate the effects of activated CAFs on 4T1 cell migration, pathway alterations during CAFs activation, and underlying mechanisms. The reversal effect of baicalein on CAFs activation and its molecular mechanism were systematically evaluated. Molecular docking and dynamics simulations were performed to assess the binding affinity and stability of baicalein with key pathway proteins. A murine orthotopic TNBC co-implantation model was established to validate the in vivo effects of baicalein on CAFs activation reversal and TME remodeling.

## 03 Results




Both CAFs activation and high PI3K expression correlated with TNBC patients poor prognosis

PI3K/Akt/mTOR activation is a novel mechanism driving CAFs activation in TNBC

Baicalein reverses CAFs activation by inhibiting the PI3K/Akt/mTOR pathway, suppresses collagen fiber formation in the tumor stroma and remodels the TME

## 04 Conclusion

In TNBC patients, CAFs activation, stroma-rich TME, and aberrant PI3K activation are interrelated and associated with poor prognosis. PI3K/Akt/mTOR pathway activation is a novel mechanism driving CAFs activation in TNBC. Baicalein reverses CAFs activation by inhibiting the PI3K/Akt/mTOR pathway, suppresses collagen fiber formation in the tumor stroma, and remodels the TME in TNBC tumor-bearing mice. This study lays a theoretical and experimental foundation for developing novel integrated Chinese and Western medicine anti-tumor strategies based on TME modulation.