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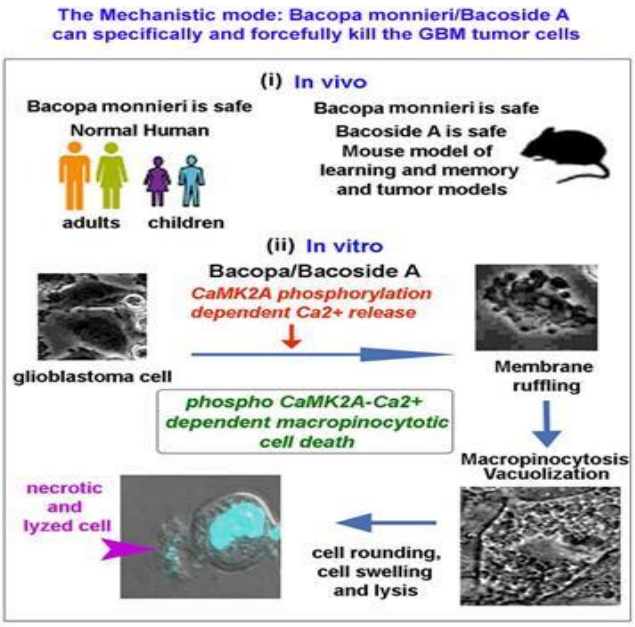
Novel insights on brain cancer therapeutics

Dr. Rashmi Mishra and her team at Rajiv Gandhi Centre for Biotechnology (RGCB), Thiruvananthapuram found that tumor cells, contrary to normal cells, are not efficient in handling excess calcium which is required for constitutive macropinocytosis and it can lead to uncontrolled fluid uptake. The information clearly hint that forcefully triggering calcium-burst in GBM cells can lead to excessive macropinocytotic uptake of extracellular fluid which may transform into irreversible hydraulic stress and cellular damage, enabling tumor eradication.



In order to test this possibility, the research team scored Indian traditional medicinal plant *Bacopa monnieri* (BM) and its bioactive component Bacoside A as a potential drug candidate to disturb the delicate calcium mechano-homeostasis of tumor cells. BM has been previously shown to activate an intracellular calcium release kinase CaMK2A, thereby can modulate calcium levels. BM and Bacoside A could indeed generate dosage associated tumor specific disturbances in the hydrostatic pressure balance of the cell *via* a mechanism involving excessive phosphorylation of calcium/calmodulin-dependent protein kinase IIA (CaMKIIA/CaMK2A) enzyme that was further involved in the release of calcium from intracellular reserves. High intracellular calcium stimulated massive macropinocytotic extracellular fluid intake causing cell hypertrophy in the initial stages, excessive

macropinosome enlargement and fluid accumulation associated organellar congestion, cell swelling, cell rounding and membrane rupture of glioblastoma cells.

All these events finally culminated into a non-apoptotic, physical non-homeostasis associated glioblastoma tumor cell death, demonstrating *Bacopa monnieri* aqueous extract and its bioactive components as promising drug candidates for the deadly brain cancer-the Glioblastoma multiforme. Dr. Mishra's future work will aim at testing this therapeutic concept in glioblastoma mouse model and directing efforts towards clinical collaborations to escalate the knowledge to translational platforms.

Glioblastoma multiforme (GBM) is the most aggressive and deadliest brain tumor, noted for low survival rates due to ineffective chemotherapies and multiple relapses. In order to develop robust therapeutics, we need to understand tumors in a newer perspective mainly as a mechanically transformed system. Why? Because tumor cells intercept so many biophysical forces and mechano-adapt to these forces to survive in harsh tumor microenvironments. Macropinocytosis is a crucial constitutive mechano-adaptive process through which both normal and tumor cells uptake excess nutrients in a fluid phase. Intriguingly, in contrast to constitutive macropinocytosis which is a 'calcium dependent' process, tumor cells were observed to predominantly rely on 'non-calcium dependent' macropinocytosis to acquire excess nutrients.

This work was published in the *Frontiers in Molecular Neuroscience* and has received recognitions at INCD 2019, IIT, Guwahati, NRSM 2019 and ACTREC, Tata Memorial Centre Kharghar, Navi Mumbai.

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