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Metabolic stress-resistant kidney cancer cells survive glucose deprivation via PGC1α-mediatedup-regulation of plasma membrane Ca2+ATPase expression

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Selection pressure generated by the evolving tumor metabolic microenvironment, particularly glucose deprivation results in the emergence of sub-clones that display enhanced capabilities of survival. In vitro, these cells showed much higher anti-apoptotic capability than their parental counterparts. In this study, we demonstrate the potential mechanisms by which these selected kidney cancer cells avoid Ca2+-induced apoptosis during glucose deprivation. The induction of plasma membrane Ca2+ ATPase (PMCA) is mainly responsible for the transport of cytoplasmic Ca2+ to the extracellular space while B-cell lymphoma 2 (BCL2) induction by calcium/calmodulin dependent protein kinase 2 alpha (CaMK2α) signaling plays key roles in the blocking of Ca2+-dependent apoptosis. Of note, all of these effects are governed by the peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α, which transcriptionally co-regulates PMCA and CaMK2α expression thereby circumventing cytoplasmic Ca2+overload induced apoptosis upon prolonged glucose deprivation. Combined treatment with 2-Deoxy-D-glucose (2DG), a metabolic inhibitor, mimicking glucose deprivation condition in mouse xenograft models and caloxin, a specific inhibitor of PMCA significantly reduced tumor growth compared to the tumors of untreated control animals and those treated with the metabolic inhibitor alone. The current study provides compelling evidence that PGC1α is a key regulator of anti-apoptosis in metabolic stress-selected cells by inducing PMCA and CaMK2α allowing survival in glucose-deprived conditions.

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Prevalence of obstetric fistula: A population-based study in rural Pakistan

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Objective: To estimate the prevalence of obstetric fistula, its duration and impact on women's daily life using robust data collection methods in a population based sample in rural Pakistan.

Design: A population-based, cross-sectional study.

Setting: A rural community in Sindh Province, Pakistan

Population: Randomly selected women aged 15 or older.

Methods: A multistage random sampling strategy was used to recruit the women. Lady Health Workers interviewed women in their own homes using a structured questionnaire to obtain symptom data. Women with symptoms of incontinence were then examined by female gynaecologists in their local health facilities to confirm obstetric fistula.

Main outcome measure: Obstetric fistula confirmed by gynaecological examination.

Results: Among the 5064 women interviewed (96% response rate), 20 cases of obstetric fistula were identified, showing a prevalence of 0.39% of all women (95% CI 0.22% to 0.57%) and 0.45% of parous women (95% CI 0.25% to 0.65%). Significantly more of the women with obstetric fistula compared with parous women without fistula were primiparae and aged less than 20. 40% of women with obstetric fistula had this for more than 5 years and 90% reported a major impact on their lives, yet only 4 had consulted a doctor 3 of whom had failed repairs.

Conclusions: The prevalence of obstetric fistula is high in rural Pakistan. Appropriate provision is needed for fistula repair to reduce the burden of the condition. Alongside this the improvement of maternity care services is urgently needed to prevent its continued occurrence.

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