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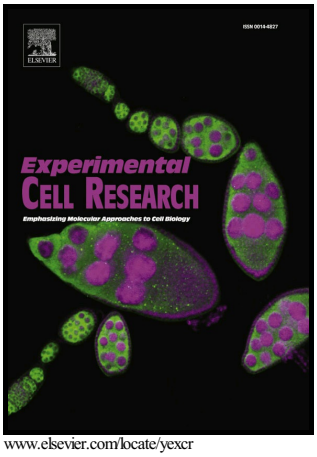

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Intracellular redox status controls spherogenicity, an *in vitro* cancer stem cell marker, in thyroid cancer cell lines

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ABSTRACT

Cancer stem cells (CSCs), a small fraction of a tumor mass, are proposed to be highly crucial for cancer initiation, recurrence and metastasis. We have recently found that aldehyde dehydrogenase (ALDH) 1A3 is a CSC marker in some thyroid cancer cell lines, whose functional activity is, however, not relevant for thyroid cancer stemness. Since previous studies on malignancies in other organs suggest that intracellular reactive oxygen species (ROS) might be a functional and targetable CSC marker, the present study was conducted to elucidate the significance of ROS as a functional CSC marker in thyroid cancer cell lines. We first found that ROS levels controlled spherogenicity; that is, ROS^{low} cells were more spherogenic than ROS^{high} cells. However, unlike typical CSCs in other cancers, CSC-like ROS^{low} cells in thyroid cancer cells were plastic and were not accompanied by de-differentiation status (*i.e.*, expression of stemness markers/thyroid-specific transcription factors) or chemo-/radio-resistance. The lower levels of ROS were functionally critical because a forced increase in ROS levels by L-buthionine-S,R-sulfoximine, an inhibitor of glutathione (GSH) synthesis, and irradiation suppressed spherogenicity. ROS levels were also correlated with the number of double strand DNA breaks determined by 53BP1 staining. Lower ROS levels appear to be a result of decreased mitochondrial oxidative phosphorylation and elevated GSH contents. Given the importance of CSC-targeted therapy for achieving long-term disease eradication by