Tumor stemness and cancer drug-resistance: role of aldehyde dehydrogenase 1A1

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CSCs (cancer stem cells) are a subtype of cancer cells sharing common properties with normal stem cells (SCs), that can initiate new tumors following injection into animal models.Recently, several studies have shown that tumor-initiating cells have CSC-like properties in a number of solid malignancies, in particular in breast cancer.CSCs are involved in metastasis and cancer relapse and can significantly affect tumor therapy. Importantly, tumor drug resistance seems to be closely related to many intrinsic or acquired properties of CSCs, such as quiescence, DNA repair ability and overexpression of anti-apoptotic proteins, drug efflux transporters and detoxifying enzymes (Vinogradov& Wei, 2012). Among these, enzyme aldehyde dehydrogenase 1A1(ALDH1A1) is associated with stem-like phenotype switching, worse clinical outcome and cell-acquired drug resistance (Charafe-Jauffret et al., 2009; Tomita et al., 2016). Aldehyde dehydrogenases (ALDHs) are family members of NAD-dependent enzymes that catalyze the oxidation of aldehydes to acids. To date, 19 ALDH members have been identified in the human genome. They are localized in the cytoplasm, mitochondria, or nucleus and have been implicated in a wide variety of biological processes, including the detoxification of exogenously and endogenously generated aldehydes and the metabolism of vitamin A, alcohol, and reactive oxygen species (Di Zhao et., al 2014).

In this work, we aimed to investigate the expression, activity and contribution of ALDH1A1 on the malignant phenotype of a panel of metastatic breast cancer cells (MCF-7, MDA-MB231, SKBR-3), representing different histotypes. The role of ALDH1A1 has been investigated by using either a selective pharmacological inhibitor for ALDH1A1, CM037, or shRNAs for its knocking down (ALDH1A1 KD). Our results indicate that ALDH1A1 is expressed in all cell lines, without any significant difference among them, while its activity is higher in SKBR-3 cells. CM037 treatment inhibited ALDH1A1 activity in a dose dependent manner, and both CM037 and ALDH1A1 knock down reduced either the basal and the serum-induced growth and clonogenic potential of breast tumor cells. Further, by using a three-dimensional tumor spheroid culture system in vitro that more closely mimics the growth characteristics of CSCsin vivo, we investigated the role of ALDH1A1 in tumorsphere formation. Pharmacological inhibition of ALDH1A1 activity and gene knock down of the enzyme significantly reduced tumor cell stemness.

In conclusion,we have characterized the expression and activity of ALDH1A1 in a series of breast cancer cell lines and set up a model of tumor cells,useful to investigate the contribution of ALDH1A1 in the control of stemness. Our final goal is to evaluate the role of stemness in cancer-drug resistance.

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