The role of ALDH^{br} BCSCs as prognostic markers and therapeutic targets in breast cancer

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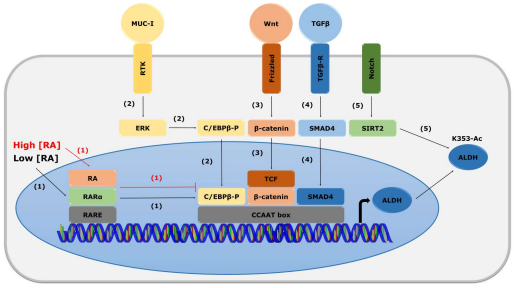
Introduction:

- The CSC theory proposes that CSCs are able to establish themselves, drive tumorigenesis giving rise to all cancer cell types, induce metastasis and recurrence, because of their self-renewal, differentiation and chemotherapy/radiotherapy resistance abilities.
- Isolation of CSCs and targeting therapies against them are needed to overcome cancer.
- ALDHs are CSC markers and ALDH^{br} CSCs selects for poor prognosis cancers.
- ALDHs are involved in the RA signalling, the self-protection against oxidative stress and the chemotherapy/radiotherapy resistance of CSCs

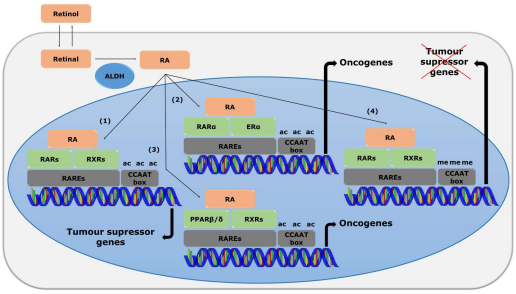
Objectives:

1. To study the role of ALDHs in BCSCs.
2. To assess ALDH^{br} BCSCs as prognostic markers in breast cancer.
3. To assess ALDH^{br} BCSCs as therapeutic targets in breast cancer.

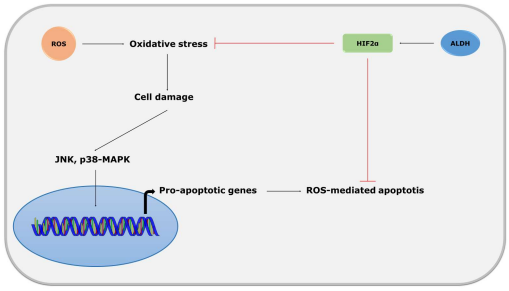
Results:



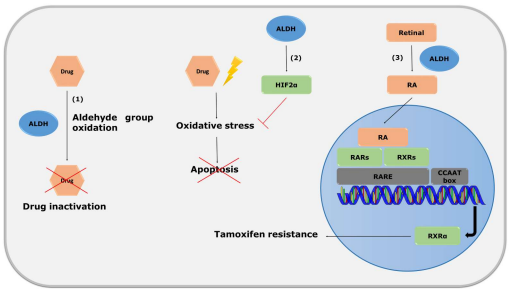
Transcriptional and post-translational regulation of ALDHs in BCSCs



The role of ALDHs in the RA signalling pathways of BCSCs



The role of ALDHs in the self-protection against oxidative stress of BCSCs



The role of ALDHs in chemotherapy/radiotherapy resistance of BCSCs

Prognostic value of ALDH^{br} BCSCs

	Marker	Prognostic value
Cui et al.	ALDH^{br}CD44+ BCSCs	Correlated with the Ki67^{+} molecular subtype of invasive breast carcinoma, which is a marker of chemotherapy resistance and, therefore, poor survival.
Marcato et al.	ALDH1A3^{br} BCSCs	Correlated with poor survival in triple-negative breast cancers.
Tiezzi et al.	ALDH^{+} BCSCs	Correlated with poor prognosis in locally advanced breast cancers
Marcato et al.	ALDH1A3^{br} BCSCs	Correlated with high proximal metastasis in high grade breast cancers
Woodward et al.	ALDH1^{+} BCSCs	Independent predictor of worse overall survival in ER^{-} breast cancers
Neumeister et al.	ALDH1^{br}CD44^{+}CD24^{-} epithelial BCSCs	Correlated with worse outcome independently of tumour grade, tumour size, ER, progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and nodal status
Khoury et al.	ALDH1A1^{+} BCSCs	Correlated with increased risk of recurrence in post-neoadjuvant chemotherapy patients with triple-negative, HER2^{+} and lymph-node status breast cancers
Charafe-Jauffret et al.	ALDH^{br} BCSCs	Independent predictor of metastasis
Zhong et al.	ALDH1^{+} BCSCs	Independent predictor of recurrence and worse disease-free survival (DFS) in invasive ductal breast cancer
Qiu et al.	ALDH1A3^{+} BCSCs	Correlated with distant metastasis and worse DFS and overall survival (OS)
Opdenaker et al.	ALDH1A3^{+} BCSCs	Correlated with tumour grade in triple-negative breast cancers
Qiu et al.	ALDH1A3^{+}CD44^{+} BCSCs	Correlated with advanced stage, distant metastasis, high tumour size and high nodal status breast cancers and predictor of worse DFS and OS independently of the treatment received

- ALDH1A3^{br} BCSCs are the best ALDH markers to predict prognosis.
- ALDH1A3^{br} BCSCs are poor prognosis markers.
- Further research is needed to adjust their prognostic value.
- Further research is needed regarding the best combination of markers.
- Further research is needed regarding the distinction between ALDH^{br} BCSCs and ALDH^{br} normal breast SCs.
- Further research is needed regarding the prognostic value of ALDHs in CTCs, DTCs and epithelial-like BCSCs.

Therapeutic target value of ALDH^{br} BCSCs

	Treatment	Target	Outcome
Bhola et al.	TGF-β type I receptor kinase inhibitor (LY2157299), a neutralizing TGF-β type II receptor antibody and SMAD4 siRNA	TGFβ signalling pathway of ALDH^{br} BCSCs in triple-negative breast cancer cell lines and mouse xenografts	Blockage of ALDH^{br} BCSCs expansion and prevention of recurrence after paclitaxel treatment
Zhao et al.	ALDH1A1 acetylation (K353) mimetic mutant	ALDH1A1 of ALDH^{br} BCSCs in breast cancer xenograft models	Tumorigenesis and tumour growth inhibition
Croker et al.	DEAB	ALDH^{br}CD44^{+} BCSCs	Long-term sensitization of ALDH^{br}CD44^{+} BCSCs to chemotherapy and radiotherapy
Wang et al.	Disulfiram	ALDHs involved in the self-protection against oxidative stress in ALDH^{br} BCSCs	Decreased stem cell properties in tumors
Allensworth et al.	Disulfiram	ALDHs involved in the self-protection against oxidative stress in ALDH^{br} BCSCs	Oxidative stress-mediated apoptosis induction
Sirchia et al.	Decitabine, a DNMT inhibitors and Trichostatin, a HDAC inhibitor and ATRA	RA signalling pathways of breast cancers	Growth inhibition both in vitro and in vivo
Nguyen et al.	Entinostat, a HDAC inhibitor, ATRA and low-dose Doxorubicin	RA signalling pathways of triple negative breast cancers	Regression of established tumour xenografts
Suman et al.	Psoralidin, an inhibitor of NOTCH1 signalling	Notch signalling pathway of ALDH^{br} BCSCs	Growth arrest in both breast SCs and BCSCs

- The combination of retinoids and epigenetic modifiers is the most promising therapy.
- Targeting against the Notch and the TGFβ signalling of ALDH^{br} BCSCs inhibits their BCSC behaviour.
- Direct targeting against ALDHs inhibits BCSC behaviour.
- Further research is needed on the previously described targets and on the targeting of other ALDH-regulatory and functional signalling pathways.
- Further research is needed regarding the distinction between ALDH^{br} BCSCs and ALDH^{br} normal breast SCs.

Conclusions:

1. ALDHs are BCSC markers tightly related with the behaviour of BCSCs, where they play a functional role in the RA-signalling pathways, the self-protection against oxidative stress and the chemotherapy/radiotherapy resistance.
2. ALDH1A3^{br} BCSCs are poor prognosis markers in breast cancer.
3. ALDH^{br} BCSCs are possible future therapeutic targets to overcome breast cancer.

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