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Review Article

Cancer Stem Cell Markers and Therapy Resistance in Triple-Negative Breast Carcinoma

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Abstract

Background: In triple-negative breast carcinoma the term cancer stem cell is applied to populations defined either by CD44 and CD24 surface phenotype or by aldehyde dehydrogenase activity.

Objective: To test whether the two marker systems identify the same cells, and whether the measurements support claims about chemoresistance, prognosis and targeted treatment.

Methods: Narrative review of marker-scoring series, functional assays, prognostic meta-analyses and one randomised trial.

Findings: The systems barely overlap: across 466 carcinomas approximately 1% of cells were both marker-positive, and the same 54 metastatic biopsies scored 34/54 for one system against 16/54 for the other. Chemotherapy raised marker-positive cells from 4.7% to 13.6% (N = 31), yet a randomised trial of 123 patients showed no benefit.

Conclusions: The evidence supports reproducible enrichment of marker-positive cells after cytotoxic therapy. It does not support treating either marker system as identifying a single resistant compartment, or as a clinical decision tool.

Keywords: Cancer stem cells; Triple-negative breast carcinoma; Aldehyde dehydrogenase; Chemotherapy resistance; Tumour heterogeneity

Introduction

Triple-negative breast carcinoma is defined by what it lacks, and the absence of oestrogen receptor, progesterone receptor and HER2 amplification leaves cytotoxic chemotherapy as the backbone of systemic treatment. The disease is not one entity: transcriptional classification separates basal-like, mesenchymal, immunomodulatory and luminal androgen receptor groups with different preclinical drug sensitivities [1]. Against that heterogeneity, the cancer stem cell hypothesis offered an appealingly simple account of why chemotherapy shrinks tumours that later regrow. A minority subpopulation with self-renewal capacity survives treatment, and the bulk that regrows is its progeny. The hypothesis entered breast oncology through the prospective isolation of tumorigenic cells by surface phenotype [2] and was extended by aldehyde dehydrogenase activity as an alternative enrichment handle [3]. Two decades later the model itself has been repeatedly revised, from a fixed hierarchy toward a plastic, context-dependent state [4,5].

This review examines a specific and consequential problem inside that literature. The phrase "cancer stem cell" is used as though it named one population, but in triple-negative disease it names at least two, and which one an investigator reports is determined by the assay chosen rather than by the tumour. The consequences run through every downstream claim. Prevalence estimates diverge by a factor of six in the same cohort. Enrichment after chemotherapy is reproducible, and among the best-supported observations in the field, yet the prognostic literature built on the same markers contradicts itself in ways that stratification and multivariate adjustment make worse rather than better. And the one randomised trial of a cancer stem cell-directed agent in metastatic triple-negative disease was flatly negative. The argument here is that these three observations are connected: an ambiguous measurement

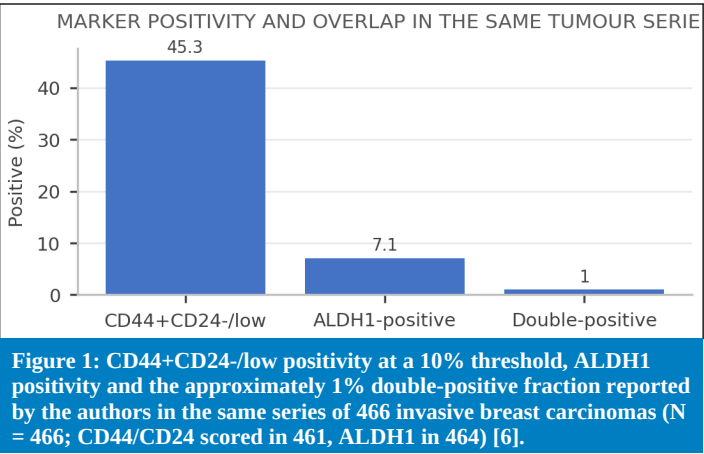
cannot support an unambiguous clinical inference.

Two marker systems that label different cells

The clearest evidence that the marker systems are not interchangeable comes from scoring both in the same tumours. In a series of 466 invasive breast carcinomas, the CD44+CD24-/low phenotype, at a threshold of at least 10% of cells, was present in 45.3% (209/461), while ALDH1 positivity was found in only 7.1% (33/464); approximately 1% of primary tumour cells were both CD44+CD24-/low and ALDH1-high, although 75.8% (25/33) of ALDH1-positive cases were also CD24-/low [6]. Two markers that are said to identify the same biological compartment therefore coincide in roughly one cell in a hundred. The discordance is not confined to primary disease. Among centrally reviewed metastatic triple-negative biopsies, ALDH-positive cells were detected in 16/54 (29.6%) and CD24-/CD44+ cells in 34/54 (63.0%) of the same set of specimens [7].

Prevalence also depends on how positivity is defined. Scoring presence rather than a percentage threshold, CD44+/CD24- cells were found in 31% of tumours (75/240 assessable of a 445-patient cohort), with the within-tumour fraction ranging from a few cells to close to 100% [8]. That range is itself the problem: a marker whose positive fraction spans two orders of magnitude across tumours is not identifying a rare cell in any consistent sense. Both systems are enriched in basal-like disease — 63% of basal-like tumours versus 30% of luminal A, 14% of SR-HER2+ and 8% of SR+HER2+ cases ($P < 0.001$), and 16/17 (94%) of BRCA1-defective tumours [8]; 76.5% (52/68) of basal-like tumours at the 10% threshold [6]. Enrichment in the subtype of interest is exactly what makes the ambiguity costly, because it is in triple-negative disease that both assays return their highest positive fractions and their weakest agreement. Within the ALDH1-positive group of that 466-tumour series, 39.4% (13/33) of cases were basal-like [6], so the two systems

converge on the same subtype while diverging on the individual cells inside it.



What the assays measure, and what they do not

The two readouts are not measuring the same kind of thing. CD44 and CD24 are surface glycoproteins scored by flow cytometry or dual immunohistochemistry, and CD24-low is a relative judgement against an internal distribution rather than an absolute cut-off. ALDEFLUOR reports enzyme activity, and ALDH1A1 immunohistochemistry reports protein abundance of one isoform; neither is a surface identity. Cell lines make the instability of the surface phenotype plain. Across 13 lines, MDA-MB-231 was 85% CD44+/CD24- and five lines exceeded 30%, while MCF-7, T47-D, MDA-MB-468, SK-BR-3, ZR-75-1, DU4475 and BT474 were minimal or absent [9]. Within basal-like lines the variation is wider still: SUM159, SUM1315 and MDA-MB-231 are more than 90% CD44+/CD24-, whereas SUM149 is only about 5% [10]. A marker that labels more than nine cells in ten cannot simultaneously be identifying a rare stem compartment.

The functional assays paired with these markers have their own artefacts. Mammosphere formation, the standard in vitro surrogate, alters the population it measures: normal human mammary epithelium forms spheres at about 4 per 1,000 cells, stable across five serial passages, but the

side-population fraction inside mammospheres reaches 27% against roughly 1% in uncultured tissue [11]. Sphere formation reflects survival in anchorage-independent suspension as much as self-renewal, and its interpretation as a stem cell readout has been challenged on those grounds [12]. Xenograft limiting dilution is the reference assay, yet its output depends on the host. In NOD/SCID recipients only 0.1% to 0.0001% of human cancer cells formed tumours, while in NOD/SCID Il2rg-/- recipients approximately 25% of unselected melanoma cells from 12 patients, and 27% of single unselected cells from 4 patients, did so [13]. Published breast tumour-initiating frequencies are commonly reported as dose series without intervals — ALDEFLUOR-positive cells from inflammatory breast cancer xenografts formed tumours at 50,000, 5,000 and 500 cells injected while ALDEFLUOR-negative cells formed none at any dose [14] — even though methods for interval estimation are long established [15]. Reporting frequencies without intervals is not a minor omission; it removes the only means of judging whether two sorted populations differ.

Table 1: The two marker systems compared by what they detect, the functional assay usually paired with them and the reported prognostic association [6,8,14,10,19,27].		
Feature	CD44+/CD24-low	ALDH1 / ALDEFLUOR
What is detected	Two surface glycoproteins; relative CD24 threshold	Enzyme activity or ALDH1A1 protein abundance
Prevalence, primary tumours	45.3% at 10% threshold; 31% by presence	7.1% of tumours positive
Basal-like enrichment	76.5% of basal-like tumours	39.4% of positive cases basal-like
Paired functional assay	Mammosphere formation; xenograft dilution	ALDEFLUOR sorting then xenograft dilution
Change with chemotherapy	4.7% to 13.6% in patients; 5-30-fold in vitro	Increased after therapy, P = 0.018
Pooled survival estimate	RR 2.32 (95% CI 1.51-3.60)	RR 2.83 (95% CI 2.16-3.67)

The deeper difficulty is that the compartment being sorted is not stable. Epithelial-mesenchymal transition generates

cells with stem-like properties [16], non-stem cells convert spontaneously to a stem-like state [17], and cell populations return to a characteristic phenotypic equilibrium after sorting [18]. A marker-defined fraction that regenerates itself from marker-negative cells cannot be treated as a fixed lineage compartment, and the interval between sorting and readout then becomes part of the measurement rather than a technical detail.

Chemotherapy enriches marker-positive cells

The enrichment observation is the most reproducible finding in this literature. In patients with HER2-negative disease receiving neoadjuvant chemotherapy, mean CD44+/CD24-low cells rose from 4.7% (95% CI 3.5-5.9) at baseline to 13.6% (95% CI 10.9-16.3) after 12 weeks ($P < .001$, $N = 31$), and mammosphere-forming efficiency in the same cohort rose from 13.3% (95% CI 6.0-20.6) to 53.2% (95% CI 42.4-64.0, $P < .001$) [19]. The comparison arm is what makes the result interpretable: 12 weeks of lapatinib in 21 patients produced no significant change, with CD44+/CD24-low moving from 10.0% to 7.5% and mammosphere efficiency from 16.1% to 10.8% [19]. Enrichment is therefore specific to cytotoxic selection rather than a generic effect of treatment or of repeat biopsy.

Independent cohorts agree. In 92 patients with stage II-III disease receiving primary systemic therapy, baseline CD44+/CD24- was a median of 5% (range 0-95%) and increased significantly after therapy ($P = 0.013$), while ALDH1 positivity at a 5% cell threshold was present in 12/92 (13%) at baseline with a median of 0% (range 0-80%) and likewise increased ($P = 0.018$) [20]. In vitro, CD44+/CD24-/ESA+ cells were enriched 5- to 30-fold in treated versus placebo-treated cultures, and surviving MDA-MB-231 cells averaged 30% after paclitaxel and 35% after 5-fluorouracil [10]. Paclitaxel raised the ALDH-positive fraction 7- to 9-fold in SUM159 triple-negative cells at 5-10 nM ($P < 0.01$), with

comparable expansion of CD44hi/PROCR+ cells in BT549 ($P < 0.01$) [21]. Residual tumours after conventional therapy — 12 docetaxel-treated and 18 letrozole-treated patient pairs — displayed mesenchymal and tumour-initiating features relative to matched pretreatment samples [22].

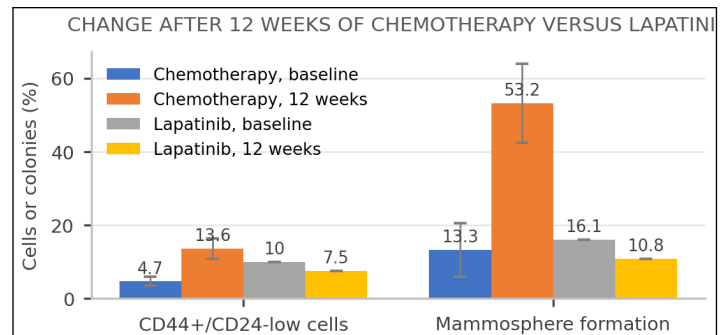


Figure 2: Marker-positive cells and mammosphere-forming efficiency before and after 12 weeks of neoadjuvant chemotherapy ($N = 31$, error bars 95% CI, $P < .001$ for both) against a lapatinib arm with no significant change ($N = 21$, no intervals reported) [19].

Enrichment, however, is compatible with more than one mechanism. Selection of a pre-existing resistant compartment is one; induction of a reversible drug-tolerant state is another [23], and single-cell sequencing of triple-negative tumours through neoadjuvant treatment has been used to separate clonal selection from transcriptional adaptation [24]. Intrinsic resistance mechanisms proposed for the marker-positive fraction include altered DNA damage response after irradiation [25] and lower reactive oxygen species with associated radioresistance [26]. A rising marker fraction alone cannot distinguish these accounts, because plasticity predicts the same measurement as selection.

The prognostic literature disagrees with itself

If marker-positive cells survive chemotherapy, their abundance should predict outcome. It does, and it does not, depending on the study. Two meta-analyses report a consistent adverse association: pooling 12 studies with 898 cases and 1,853 controls gave an overall survival relative risk of 2.83 (95% CI 2.16-3.67, $P < 0.001$) for ALDH1

positivity and 2.32 (95% CI 1.51-3.60, $P < 0.001$) for CD44+/CD24-/low [27]; pooling 15 publications and 16 studies across 3,274 patients gave a survival odds ratio of 2.58 (95% CI 2.05-3.23, $P = 0.000$, $I^2 = 38.0\%$) and a disease-free survival odds ratio of 2.16 (95% CI 1.68-2.79, $P = 0.000$, $I^2 = 0.0\%$) for ALDH1A1 [28]. In 109 inflammatory breast cancers followed for a median of 67 months, ALDH1 was expressed in 34% of tumours and carried a multivariate overall survival hazard ratio of 2.7 (95% CI 1.48-4.93, $P = 0.012$), with median survival of 27 months in ALDH1-positive versus 63 months in ALDH1-negative disease [14].

Table 2: Study-by-study prognostic associations reported for each marker system, with the population examined, showing the disagreement between pooled and stratified analyses [8,29,30,27,28,31,20].			
Study	Population (N)	Reported association	Direction
Honeth 2008	240 tumours	No correlation with 5-year distant DFS	Null
Abraham 2005	Not stated	May not predict outcome; favours metastasis	Mixed
Idowu 2012	Not stated	More abundant in TNBC; poor outcome	Adverse
Zhou 2010	898 cases, 1,853 controls	OS RR 2.32 and 2.83	Adverse
Liu 2014	3,274 patients	OS OR 2.58; DFS OR 2.16	Adverse
Kida 2016	653 tumours, 234 neoadjuvant	Prognostic in luminal only; pCR 13.5% vs 30.3%	Null in TNBC
Lee 2011	92 patients	DFS $P = 0.043/0.041$; not independent	Null adjusted

The primary studies are less unanimous. No significant correlation was found between CD44+/CD24- status and distant disease-free survival at five years in 240 tumours [8]; the prevalence of CD44+/CD24-/low cells may not be associated with clinical outcome while still favouring distant metastasis [29]; and the same phenotype has been reported as more abundant in triple-negative disease and associated with poor outcome [30]. These cannot all be correct, and the pooled estimates rest on the same small series whose thresholds differ — presence of any positive cell in one study, at least 10% of cells in another.

Two studies matter most because they interrogate rather than pool. Stratifying 653 invasive breast cancers, of which 234 received neoadjuvant chemotherapy, ALDH1 positivity was associated with shorter disease-free ($P < 0.001$) and overall survival ($P = 0.044$) overall and within luminal disease, but was not significantly prognostic in triple-negative or HER2-enriched disease; in the same series pathological complete response occurred in 13.5% of ALDH1-positive versus 30.3% of ALDH1-negative cases ($P = 0.003$), a correlation strongest in triple-negative tumours ($P = 0.003$) [31]. ALDH1 thus behaves as a predictive marker of chemoresistance precisely where it fails as a prognostic marker. In the 92-patient primary systemic therapy cohort, patients whose CD44+/CD24-fraction increased had shorter disease-free survival ($P = 0.043$), as did those whose ALDH1 fraction increased ($P = 0.041$), yet neither change remained independent on multivariate analysis; only ypT stage did, with a hazard ratio of 4.82 (95% CI 1.28-18.18, $P = 0.020$) [20]. Marker enrichment may be a marker of residual disease burden rather than of a distinct resistant compartment.

Targeting the compartment has not worked

The clinical test of the hypothesis has been performed and returned a negative result. In fRida, a randomised placebo-controlled phase 2 trial of front-line paclitaxel with or without the CXCR1/2 inhibitor reparixin in metastatic triple-negative disease, 123 patients were randomised (62 and 61). Median progression-free survival was 5.5 versus 5.6 months, hazard ratio 1.13 (95% CI 0.71-1.80, $P = 0.5996$), and median overall survival 16.0 versus 17.4 months, hazard ratio 1.09 (95% CI 0.68-1.75, $P = 0.7059$), with 38/62 and 34/61 deaths at analysis [7]. The preceding window-of-opportunity study in operable HER2-negative disease enrolled 20 patients, 17 evaluable for stem cell endpoints; ALDH-positive cells fell by at least 20% in 4/17 and CD24-/CD44+ cells in 9/17, but the flow cytometry findings could not be confirmed by immunofluorescence because of the very low number of

such cells, and the authors state that the clinical relevance of a 20% reduction remains unknown [32]. Target engagement was neither demonstrated by a second method nor anchored to a validated endpoint, and the phase 2 trial that followed had no reliable pharmacodynamic threshold to aim at. Combination strategies retain preclinical support — TGF-beta receptor inhibition reduced tumour-initiating cell frequency alone and with paclitaxel in a triple-negative xenograft (both $P < 0.01$) [21] — and resistance to sequential paclitaxel and epirubicin has been linked to ALDH1 expression [33], but no positive randomised result exists.

Conclusion

The evidence assembled here is internally coherent only if the ambiguity is made explicit. Two marker systems label largely different cells in the same tumours, overlapping in approximately 1% of cells across 466 carcinomas [6] and scoring 34/54 versus 16/54 in the same metastatic biopsies [7]. Cytotoxic chemotherapy reliably enriches marker-positive and sphere-forming cells against a null targeted-therapy arm [19], but the mechanism is undetermined between selection and induced plasticity. Prognostic association is robust in pooled analyses [27,28] and absent where it is tested within triple-negative disease [31] or adjusted for stage [20]. A single randomised trial of a stem cell-directed agent showed no benefit [7]. Recording that disagreement is more useful than resolving it by preference. What would change the position is procedural rather than conceptual: a pre-specified scoring threshold, demonstrated inter-laboratory reproducibility of ALDEFLUOR and dual immunohistochemistry, tumour-initiating frequencies reported with intervals [15], and prospective validation in a triple-negative cohort with the endpoint fixed in advance. Until then, "cancer stem cell" in triple-negative breast carcinoma names an assay result, not a cell.

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