Commentary

iMedPub Journals
www.imedpub.com

Insights in Stem Cells

2017
Vol.3 No.1:2

The Molecular Circuitry Linking Cancer Stem Cells and Chemo-Resistance

Fatemeh Zolghadr[1], Shaan Kanagalingam[1] and Naisana S Asli[1,2,3*]

[1]Department of Life Sciences, Faculty of Dentistry, University of Sydney, Westmead Hospital, Westmead NSW 2145, Australia.

[2]Department of Oral Pathology and Oral Medicine, The Cellular and Molecular Pathology Research Unit, Faculty of Dentistry, University of Sydney, Westmead Hospital, Westmead NSW 2145, Australia

[3]Sydney Medical School, University of Sydney, Westmead NSW 2145, Australia

[*]**Corresponding author**: Naisana S. Asli, Department of Life Sciences, Faculty of Dentistry, University of Sydney, Westmead Hospital, Westmead NSW 2145, Australia, Tel: +02 88904818; E-mail: naisana.seyedasli@sydney.edu.au

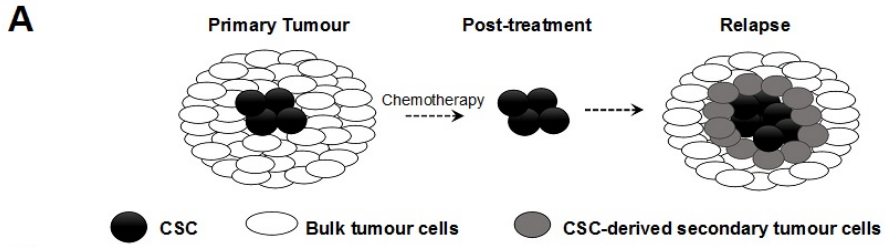
Received date: August 13, 2017, **Accepted date:** September 15, 2017, **Published date:** September 20, 2017.

Citation: Zolghadr F, Kanagalingam S, Asli NS (2017) The Molecular Circuitry Linking Cancer Stem Cells and Chemo-resistance. Insights in Stem Cells Vol.3:No.2:2.

Commentary

The uncontrolled cellular growth known as cancer has been the evil companion of the human race throughout history with evidence of tumors dating back to fossilized bones and mummies in ancient Egypt. The deadly friend has ever since provoked immediate treatment measures, and hence research and development of novel therapies. Despite all advances however, the disease is far from "treatable" yet scoring the highest death rate in the modern world. Chemotherapy, the mainstream cancer treatment with various chemical reagents primarily targets actively proliferating cells, commonly through inhibition of the mitotic machinery or DNA replication, leading to downstream apoptotic events. The clinical application of chemotherapeutic agents is commonly perplexed by the fact that despite initial remission, most cancers show poor prognosis with metastatic and/or chemo-resistant relapse. Clinical and experimental evidence suggest a key role for the heterogeneous nature of tumours in this context [1,2]. We and others have defined multiple levels of heterogeneity for tumours, both at the levels of mutational landscape, and cellular phenotypes where independent of genetics, tumour cells cluster into functional subgroups displaying distinct molecular and cellular behavioural outcomes [3-7]. A key compartment of tumour heterogeneity, is a cluster of stem-like cells known as cancer stem cells (CSC), that have the capacity to self-renew and form the entirety of the tumour, once isolated [8-10]. Cancer stem cells are functionally implicated in chemotherapy resistance, where they often evade/resist the cytotoxic effects of chemotherapy, survive treatments and potentially seed secondary relapsed tumours [11] (**Figure 1A**). The molecular landscape of resistance to chemotherapy is yet to be fully delineated. Here, we would like to focus on specific markers of the cancer stem cell compartment, and ask whether they directly contribute to chemo-resistant outcomes (**Figure 1B**). Cancer stem cells have been isolated from a number of tumours, based on the expression of specific cell surface antigens known as cluster of differentiation (CD). Experimental evidence supports a CD signature for CSCs that majorly involves expression of one or a combination of CD133, CD24 and CD44 antigens among others, though with little consensus between different tumours [12]. CD44 was shown to directly link to a chemo-resistant phenotype in T-cell acute lymphoblastic leukemia, by induction of a drug efflux activity [13]. Moreover, the ligand-activated CD44 pathway directly links to downstream survival mechanisms involving the MAP kinase pathway, leading to increased genomic stability, and enhanced repair machinery [14]. Apart from the surface antigen signatures, CSCs are as well marked by specialized classes of transcription factors linking to downstream stem cell-associated characters. Cancer stem cells express basic stem cell transcription factors including Oct4, Nanog and Sox2 in common with embryonic and some adult stem cells [15]. Oct4 inactivates the key cell cycle regulator protein, retinoblastoma (Rb) and enhances the mitotic stability in ovarian carcinoma cells, thus impairing the apoptotic response pathway during chemotherapy [16].

The other stem cell transcription factor Nanog, is activated downstream of CD44-mediated signalling, and together with Stat3, reduces the PDCD4 tumour suppressor protein, leading to upregulation of survival proteins, and chemo-resistance in head and neck squamous carcinoma [17]. Unlike Oct4 and Nanog that are mostly implicated in genomic stability, Sox2 regulates the key membrane transporter ABCG2, which is often implicated as a major factor in drug efflux and chemo-resistance [18]. Adult and cancer stem cells as well as express members of the aldehyde dehydrogenase 1 (ALDH1) enzyme family including ALDH1A1, ALDH1A2 and ALDH1A3. These enzymes are known to detoxify a variety of endogenous and exogenous aldehydes involving some commonly used anticancer drugs like oxazaphosphorines [19,20]. Indeed, transcriptional activation of ALDH1 has been linked to poor cancer prognosis and acquired drug resistance [21].



B

CSC Marker Category	Examples of Chemo-resistance Mechanisms
Surface Markers (CD)	**CD44:** Activation of MAP kinase pathway leading to genomic stability & enhanced repair machinery; Upregulation of survival proteins (through Nanog-Stat3 pathway) **ALDH1:** Detoxification of anticancer drugs.
Stem Cell TFs	**Oct4:** Inactivation of Retinoblastoma protein and increase in mitotic stability **Nanog:** Upregulation of survival proteins (with Stat3) **Sox2:** Induction of ABCG2 membrane transporter
EMT TFs	**Snail:** Regulation of cell death and stem cell maintenance pathways; Increase of P-gp expression and/or inhibition of p53- induced apoptosis **Slug:** Increase of P-gp expression and/or inhibition of p53- induced apoptosis

Figure 1 CSC pathways directly affect chemo-resistance; **A)** The CSC model of chemotherapy resistance. Note the difference between cellular compartments in primary and secondary/relapsed tumours. **B)** Summary of CSC-related chemo-resistance pathways.

Apart from the above-mentioned CSC-specific cell surface markers and transcription factors, cancer stem cells often demonstrate a state of reversible cell cycle dormancy known as cell cycle quiescence. This state per se can potentially resist/evade a broad range of anticancer drugs, as they are often targeted against the proliferating compartments in the tumours [22,23].

Cancer stem cells are as well enriched with the molecular signature that is involved in a developmentally-conserved process known as epithelial to mesenchymal transition (EMT) [24]. Major EMT transcription factors include Snail, Slug, Twist and Zeb and their related subtypes [25]. Most EMT TFs are shown to associate with poor tumour prognosis and chemotherapy resistance [26-29]. In breast cancer cells, Snail-induced EMT contributes to drug resistance through regulating genes involved in cell death and stem cell maintenance [30]. Moreover, Snail and Slug contribute to the resistance of breast and ovarian tumour cells to multiple chemotherapy drugs by increasing the expression of the drug efflux transporter P-glycoprotein (P-gp) and/or inhibiting p53-induced apoptosis [31,32].

The direct role of CSC-related factors at various levels of chemotherapy response strongly suggests a key function for this compartment and its associated molecular machinery in the therapy evasion/resistance. The CSC characters are assigned through an orchestrated regulatory network involving the pathways mentioned above, and signaling cues from other cells within the tumour stroma and additional systemic factors [33]. The molecular machinery is, on the other hand, permanently fine-tuned in dialogue with the dynamic tumour micro-environment. A thorough understanding of the spatial and temporal tumour dynamics is therefore, absolutely essential for the design and development of more directed therapeutics.

References

1. Bilen MA, Hess KR, Campbell MT, Wang J, Broaddus RR, et al. (2016) Intratumoral heterogeneity and chemoresistance in nonseminomatous germ cell tumor of the testis. Oncotarget 7: 86280-86289.
2. Jacoby MA, Duncavage EJ, Walter MJ (2015) Implications of tumor clonal heterogeneity in the era of next-generation sequencing. Trends Cancer 1: 231-241.
3. Joun GFH, Asli NS (2017) Cancer cell properties shape along metabolic activity in human epithelial carcinoma. Stem Cell: Adv Res Ther 2017: 1-5.
4. Asli NS (2016) Molecular dissection of intra-tumoral heterogneity in human epithelial carcinoma. J Stem Cell Res Medi 1: 69-70.
5. Singh RK, Dhadve A, Sakpal A, De A, Ray P (2016) An active IGF-1R-AKT signaling imparts functional heterogeneity in ovarian CSC population. Sci Rep 6: 36612.
6. Zhang M, Tsimelzon A, Chang CH, Fan C, Wolff A, et al. (2015) Intratumoral heterogeneity in a Trp53-null mouse model of human breast cancer. Cancer Discov 5: 520-533.
7. Derenzini E, Iacobucci I, Agostinelli C, Imbrogno E, Storlazzi CT, et al. (2015) Therapeutic implications of intratumor

heterogeneity for TP53 mutational status in Burkitt lymphoma. Exp Hematol Oncol 4: 24.

8. Lindeman GJ, Visvader JE (2010) Insights into the cell of origin in breast cancer and breast cancer stem cells. Asia Pac J Clin Oncol 6: 89-97.
9. Kreso A, Dick JE (2014) Evolution of the cancer stem cell model. Cell Stem Cell 14: 275-291.
10. Nassar D, Blanpain C (2016) Cancer stem cells: Basic concepts and therapeutic implications. Annu Rev Pathol 11: 47-76.
11. Steg AD, Bevis KS, Katre AA, Ziebarth A, Dobbin ZC, et al. (2012) Stem cell pathways contribute to clinical chemoresistance in ovarian cancer. Clin Cancer Res 18: 869-881.
12. Medema JP (2013) Cancer stem cells: The challenges ahead. Nat Cell Biol 15: 338-344.
13. Hoofd C, Wang X, Lam S, Jenkins C, Wood B, et al. (2016) CD44 promotes chemoresistance in T-ALL by increased drug efflux. Exp Hematol 44: 166-171.
14. Herishanu Y, Gibellini F, Njuguna N, Hazan-Halevy I, Keyvanfar K, et al. (2008) CD44 Signaling via PI3K/AKT and MAPK/FRK pathways protects CLL cells from spontaneous and drug induced apoptosis. Blood 112: 203.
15. Amini S, Fathi F, Mobalegi J, Sofimajidpour H, Ghadimi T, et al. (2014) The expressions of stem cell markers: Oct4, Nanog, Sox2, nucleostemin, Bmi, Zfx, Tcl1, Tbx3, Dppa4, and Esrrb in bladder, colon, and prostate cancer, and certain cancer cell lines. Anat Cell Biol 47: 1-11.
16. Comisso E, Scarola M, Rosso M, Piazza S, Marzinotto S, et al. (2017) OCT4 controls mitotic stability and inactivates the RB tumor suppressor pathway to enhance ovarian cancer aggressiveness. Oncogene 36: 4253-4266.
17. Bourguignon LY, Wong G, Earle C, Chen L (2012) Hyaluronan-CD44v3 interaction with Oct4-Sox2-nanog promotes miR-302 expression leading to self-renewal, clonal formation, and cisplatin resistance in cancer stem cells from head and neck squamous cell carcinoma. J Biol Chem 287: 32800-32824.
18. Lee SH, Oh SY, Do SI, Lee HJ, Kang HJ, et al. (2014) SOX2 regulates self-renewal and tumorigenicity of stem-like cells of head and neck squamous cell carcinoma. Br J Cancer 111: 2122-2130.
19. Sladek NE, Landkamer GJ (1985) Restoration of sensitivity to oxazaphosphorines by inhibitors of aldehyde dehydrogenase activity in cultured oxazaphosphorine-resistant L1210 and cross-linking agent-resistant P388 cell lines. Cancer Res 45: 1549-1555.
20. Hilton J (1984) Role of aldehyde dehydrogenase in cyclophosphamide-resistant L1210 leukemia. Cancer Res 44: 5156-5160.
21. Tomita H, Tanaka K, Tanaka T, Hara A (2016) Aldehyde dehydrogenase 1A1 in stem cells and cancer. Oncotarget 7: 11018-11032.
22. Francescangeli F, Patrizii M, Signore M, Federici G, Di Franco S, et al. (2012) Proliferation state and polo-like kinase1 dependence of tumorigenic colon cancer cells. Stem Cells 30: 1819-1830.
23. Chen J, Li Y, Yu TS, McKay RM, Burns DK, et al. (2012) A restricted cell population propagates glioblastoma growth after chemotherapy. Nature 488: 522-526.
24. Shibue T, Weinberg RA (2017) EMT, CSCs, and drug resistance: The mechanistic link and clinical implications. Nat Rev Clin Oncol.
25. Chaffer CL, San Juan BP, Lim E, Weinberg RA (2016) EMT, cell plasticity and metastasis. Cancer Metastasis Rev 35: 645-654.
26. Shrader M, Pino MS, Brown G, Black P, Adam L, et al. (2007) Molecular correlates of gefitinib responsiveness in human bladder cancer cells. Mol Cancer Ther 6: 277-285.
27. Wang J, Li L, Zhang K, Yu Y, Li B, et al. (2013) Characterization of two novel cell lines with distinct heterogeneity derived from a single human bile duct carcinoma. PLoS One 8: e54377.
28. Lee G, Hall III RR, Ahmed AU (2016) Cancer stem cells: Cellular plasticity, niche, and its clinical relevance. J Stem Cell Res Ther 6.
29. Zheng X, Carstens JL, Kim J, Scheible M, Kaye J, et al. (2015) Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer. Nature 527: 525-530.
30. De Queiroz Crusoe E, Higashi F, Martinez GA, Barros JC, Bellesso M, et al. (2016) Is it feasible to use granulocyte-colony stimulating factor alone to mobilize progenitor cells in multiple myeloma patients induced with a cyclophosphamide, thalidomide and dexamethasone regimen? Rev Bras Hematol Hemoter 38: 302-309.
31. Bie Q, Jin C, Zhang B, Dong H (2017) IL-17B: A new area of study in the IL-17 family. Mol Immunol 90: 50-56.
32. Kurrey NK, Jalgaonkar SP, Joglekar AV, Ghanate AD, Chaskar PD, et al. (2009) Snail and slug mediate radioresistance and chemoresistance by antagonizing p53-mediated apoptosis and acquiring a stem-like phenotype in ovarian cancer cells. Stem Cells 27: 2059-2068.
33. Zhao J (2016) Cancer stem cells and chemoresistance: The smartest survives the raid. Pharmacol Ther 160: 145-158.