Stem Cell Rev and Rep (2011) 7:797–798
DOI 10.1007/s12015-011-9267-1

Claudins and Cancer Stem Cells

Kursad Turksen

Published online: 28 April 2011

Abstract It is now believed that most epithelial tumors are maintained by a subpopulation of cells called cancer stem cells (CSCs) or tumor initiating cells (TICs) with stem cell-like properties, including self-renewal and multilineage differentiation capacity. Recently new insights into this population have emerged in certain epithelial tumor types, including their Claudin^{low} phenotype and its importance to the epithelial-mesenchymal transition (EMT) process. Taken together, CSCs, EMT and Claudins appear to constitute an *axis-of-evil* in cancer, for which better understanding may lead to new therapeutic platforms.

Keywords Claudin · Cancer stem cells · Epithelial mesenchymal transition · Self renewal · Epithelia · Breast cancer

There's something happening here
What it is ain't exactly clear
Buffalo Springfield

The concept of cancer stem cells (CSCs) or tumor initiating cells (TICs) as a subpopulation of cells with self-renewal and multilineage differentiation capacity as well as ability to give rise to tumors has gained acceptance during the last several years as data from both in vitro and in vivo approaches accumulate [1–5]. Understanding the biology of this subpopulation of cells will provide improvements to cancer therapeutics.

K. Turksen (✉)
Regenerative Medicine Program, Sprott Centre for Stem Cell Research at the Ottawa Hospital Research Institute,
501 Smyth Road-CCW5226,
Ottawa, ON K1Y 8L6, Canada
e-mail: kturksen@ohri.ca

Amongst the best-studied and better understood CSCs are those of epithelial-based tissues such as those seen in breast cancer. The presence and enrichment of triple-negative breast cancer (TNBC) cells - defined by the lack of protein expression of estrogen receptor (ER), progesterone receptor (PR) and the absence of HER2 protein overexpression - in breast cancer patients after common treatments, indicates their intrinsic therapeutic resistance [6–9]. Importantly, global gene expression analysis of these cells indicates a transcription "signature" with a non-basal cell expression profile, or the recently identified "Claudin^{low}" subtypes [10].

Claudins are integral membrane proteins, identified first approximately 13 years ago, and now known to be crucial for formation of tight junctions [11, 12]. The Claudin family comprises 27 members [13], ranging in size from 22 to 27 kD and topologically categorized into the four transmembrane protein class with the carboxyl-terminus in the cytoplasm and two extracellular loops [14]. The expression pattern of the Claudin proteins is developmentally-regulated and tissue-specific, imparting tissue-specific heterogeneity to tight junction function, i.e., ion selectivity, and strength and tightness of the junction [15]. However, most tissues express multiple Claudins that can interact in either a homotypic or heterotypic fashion to form the tight junction strand [16]. Concomitant with differentiation, cells acquire functional tight junctions and such features as polarization [14]. Although the full Claudin expression profile in tissues is still not well characterized due to lack of specific antibodies for every known Claudin, nevertheless it is now clear that changes in their expression occur in various tumors, and notably coincide with changes in solid tumor initiation and progression [17–19]. Accumulating data support the view that Claudins are important markers - if not functionally important harbingers - of the changes and reflective of both the biochemical and functional changes that are occurring in the epithelium.

It is notable that a differentiation hierarchy exists across all breast cancers and the Claudin profile is distinctly different from normal epithelia [18, 20–22]. Claudin^{low} tumors are characterized by the low to absent expression of luminal differentiation markers, high enrichment for EMT markers, expression of immune response genes and most closely resembles the mammary epithelial stem cell suggesting that Claudin^{low} cells may arise from more immature stem or progenitor cells and comprise the CSC [10, 22, 23]. These observations have been complimented by data from a panel of breast cancer cell lines and genetically engineered mouse models [22].

Thus, the Claudin^{low} phenotype may be of particular significance. That breast CSCs exhibit a distinct Claudin profile different from the normal mature epithelia and more like mammary epithelial stem cells is interesting not just from a stem cells biology point of view but in considering how to target these cells for effective therapies. What do we know about regulation of the EMT switch or the developmental switch to a Claudin^{low} phenotype? Known inducers of the EMT include several transcription factors (TFs), such as Goosecoid, Snail, and Twist, as well as secreted TGF-beta1 [21, 24, 25]. Each of these factors is capable, on its own, of inducing an EMT in the human mammary epithelial (HMLE) cell line, accompanied by upregulation of expression of stem cell markers, suggesting that there may be a direct link between the EMT and the gain of CSC properties [21, 22]. Notably, it is also emerging that EMT-inducing molecules also control the expression of Claudins, suggesting that Claudins are the missing link in the EMT and acquisition of the CSC phenotype [26]. A critical issue from a therapy point of view is that the expression of stem and EMT markers in CSCs is associated with resistance to conventional anti-cancer therapies and treatment failure, highlighting the urgency of improving tools for detecting and eliminating minimal residual disease. Thus, platforms to screen for and generate better understanding of the link between regulation and dysregulation of expression of Claudins and EMT are required.

Acknowledgements We are grateful to Dr. Jane Aubin for critical reading of this commentary and providing continuous intellectual support for our work. Our work on Claudins has been supported by CIHR.

References

1. Sloma, I., Jiang, X., Eaves, A. C., & Eaves, C. J. (2010). *Leukemia, 24*, 1823–1833.
2. Maund, S. L. & Cramer, S. D. (2010). *Stem Cell Rev.*
3. Lathia, J. D., Venere, M., Rao, M. S., & Rich, J. N. (2010). *Stem Cell Rev.*
4. Regenbrecht, C. R., Lehrach, H., & Adjaye, J. (2008). *Stem Cell Reviews, 4*, 319–328.
5. Cobaleda, C., Cruz, J. J., Gonzalez-Sarmiento, R., Sanchez-Garcia, I., & Perez-Losada, J. (2008). *Stem Cell Reviews, 4*, 67–79.
6. McDermott, S. P., & Wicha, M. S. (2010). *Mol Oncol, 4*, 404–419.
7. Iwase, H., Kurebayashi, J., Tsuda, H., Ohta, T., Kurosumi, M., Miyamoto, K., et al. (2010). *Breast Cancer, 17*, 118–124.
8. Yamamoto, Y., Ibusuki, M., Nakano, M., Kawasoe, T., Hiki, R., & Iwase, H. (2009). *Breast Cancer, 16*, 260–267.
9. Carotenuto, P., Roma, C., Rachiglio, A. M., Botti, G., D'Alessio, A., & Normanno, N. (2010). *Critical Reviews in Eukaryotic Gene Expression, 20*, 17–34.
10. Perou, C. M. (2011). *The Oncologist, 16*(Suppl 1), 61–70.
11. Furuse, M., Sasaki, H., Fujimoto, K., & Tsukita, S. (1998). *The Journal of Cell Biology, 143*, 391–401.
12. Turksen, K., & Troy, T. C. (2001). *Developmental Dynamics, 222*, 292–300.
13. Mineta, K., Yamamoto, Y., Yamazaki, Y., Tanaka, H., Tada, Y., Saito, K., et al. (2011). *FEBS Letters, 585*, 606–612.
14. Turksen, K., & Troy, T. C. (2004). *Journal of Cell Science, 117*, 2435–2447.
15. Turksen, K., & Troy, T. C. (2002). *Development, 129*, 1775–1784.
16. Krause, G., Winkler, L., Mueller, S. L., Haseloff, R. F., Piontek, J., & Blasig, I. E. (2008). *Biochimica et Biophysica Acta, 1778*, 631–645.
17. Morin, P. J. (2005). *Cancer Research, 65*, 9603–9606.
18. Lanigan, F., McKiernan, E., Brennan, D. J., Hegarty, S., Millikan, R. C., McBryan, J., et al. (2009). *International Journal of Cancer, 124*, 2088–2097.
19. Hewitt, K. J., Agarwal, R., & Morin, P. J. (2006). *BMC Cancer, 6*, 186.
20. Blackman, B., Russell, T., Nordeen, S. K., Medina, D., & Neville, M. C. (2005). *Breast Cancer Research, 7*, R248–R255.
21. Taube, J. H., Herschkowitz, J. I., Komurov, K., Zhou, A. Y., Gupta, S., Yang, J., et al. (2010). *Proceedings of the National Academy of Sciences of the United States of America, 107*, 15449–15454.
22. Prat, A., Parker, J. S., Karginova, O., Fan, C., Livasy, C., Herschkowitz, J. I., et al. (2010). *Breast Cancer Research, 12*, R68.
23. Hennessy, B. T., Gonzalez-Angulo, A. M., Stemke-Hale, K., Gilcrease, M. Z., Krishnamurthy, S., Lee, J. S., et al. (2009). *Cancer Research, 69*, 4116–4124.
24. Moreno-Bueno, G., Portillo, F., & Cano, A. (2008). *Oncogene, 27*, 6958–6969.
25. Creighton, C. J., Chang, J. C., & Rosen, J. M. (2010). *Journal of Mammary Gland Biology and Neoplasia, 15*, 253–260.
26. Martinez-Estrada, O. M., Culleres, A., Soriano, F. X., Peinado, H., Bolos, V., Martinez, F. O., et al. (2006). *The Biochemical Journal, 394*, 449–457.