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Inhibition of the Sonic Hedgehog pathway using small molecule inhibitors: Targeting colon cancer stem cells

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Introduction: Cancer stem cells (CSCs) a small sub-population of solid tumours are proposed to initiate tumorigenesis and to provide a source of metastatic cells. In being resistant to different therapies, they may proliferate and repopulate tumours, leading to patient relapse. As the Sonic Hedgehog pathway (SHH) is important in stem cell survival, we assess here its regulatory role in colon CSC's, targeting it with small molecule inhibitors.

Methods: In the present study, CSC's were isolated from HT29 and DLD1 colon adenocarcinoma cells using the CD133 cell surface protein. These cells were characterized via their expression of key stem cell markers using immunofluorescence microscopy. Using real time cell impedance assays, the growth patterns of CSC's (CD133+) in comparison to non-stem cells (CD133 negative) showed differences in growth rates. Cellular response to the Hedgehog (Hh) inhibitors, cyclopamine and the synthetic analogue SANT-2 were evaluated, as compared to the control molecule tomatidine.

Results: Cyclopamine and SANT-2, antagonists of smoothened (SMO), significantly decreased cell adhesion of both DLD1 and HT29 CSC's, relative to untreated cells; and invasion of the DLD1 and HT29 CSC's through a laminin matrix was significantly retarded with treatment; also, SANT-2 impeded cell migration into the cell free areas of scratch assays, in both DLD1 and HT29 CSC's. In summary, we report here the presence of an active SHH pathway in CD133+ colon CSCs.

Conclusion: Moreover, since inhibition of this pathway clearly impeded cell adhesion, invasion and migration, small molecule inhibitors targeting the SHH pathway appear to be highly promising therapeutic tools for the treatment of metastatic colon CSC's.

Biography

Aadilah Omar obtained her PhD in 2015 from The University of the Witwatersrand. She is currently a Postdoctoral Researcher in Dr. Clement Penny's Oncology Research Laboratory at the University of the Witwatersrand and is continuing her research in Oncology. She has published several papers on the topic and submitted an original publication with her PhD findings. She is a member of the Golden Key Society and continues to work closely with the Cancer Association of South Africa in various fund raising initiatives.

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