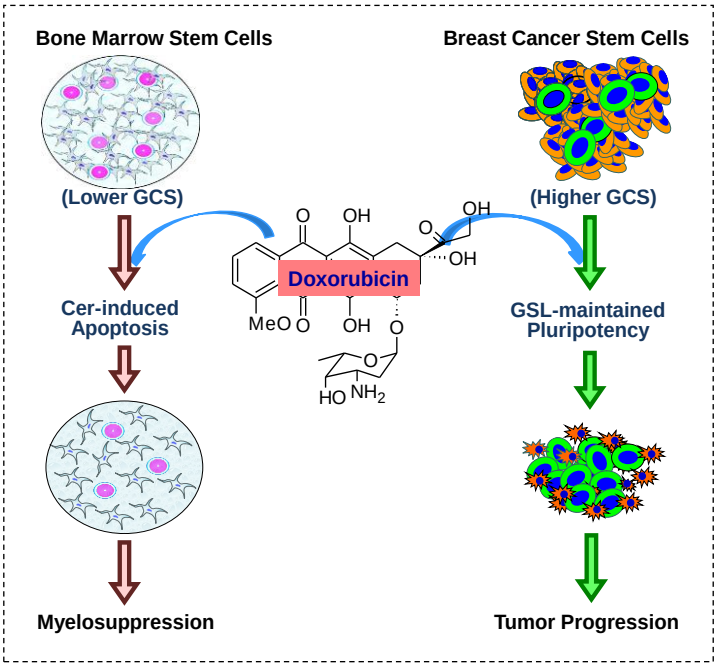
Principal Investigator: Yong-Yu Liu

Grant Title: Globo-series glycosphingolipids and the stemness of cancer stem cells

Abstract

Cancer stem cells are distinguished from normal adult stem cells by tumorous behaviors, even though both almost share the same pluripotent property or stemness. Glycosphingolipid (GSL) synthesis, which is regulated by glucosylceramide synthase (GCS), is crucial for embryonic stem cells. Among Globo series GSLs (Gb-GSLs), globopentaosylceramide (Gb5) and monosialyl Gb5 (MSGb5) are state-specific embryonic antigen-3 (SSEA-3) and -4 (SSEA-4), and are frequently used with other markers to identify embryonic stem cells. However, little is known about whether Gb-GSLs are involved in, and how Gb-GSLs modulate BCSCs. The objective of this proposal is to determine the role of Gb-GSLs in regulating BCSCs. With the Mizutani's grant, we have demonstrated that ceramide glycosylation catalyzed by GCS is enhanced in BCSCs, but not in normal mammary epithelial stem cells, and it maintains tumorous pluripotency of BCSCs. With stem cell sorting, gene manipulation, MDLDI-MS/MS analysis and animal study, it is found that enhanced ceramide glycosylation and globotriosylceramide (Gb3) correlate well with the numbers of BCSCs in breast cancer cell lines. In BCSCs sorted with $CD44^{+}/ESA^{+}/CD24^{-}$ markers, Gb3 activates cSrc/β-catenin signaling and upregulates the expression of fibroblast growth factor-2 (FGF-2), CD44 and Oct-4 enriching tumorigenesis. Conversely, silencing GCS expression disrupts Gb3 synthesis, and selectively decreases BCSCs through deactivation of cSrc/β-catenin signaling (Gupta et al., 2012). Interestingly, our study also showed that due to the different levels of GCS, doxorubicin eliminates bone marrow stem cells, but expands BCSCs in mice (Bhinge et al., 2012). These findings highlight the unexploited role of ceramide glycosylation, particular Gb3 of Gb-GSLs in selectively maintaining the tumorous pluripotency of BCSCs. It speculates that disruption of ceramide glycosylation or Gb3 is a useful approach targeting BCSCs.



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