Notch1 Stimulation Induces a Vascularization Switch With Pericyte-Like Cell Differentiation of Glioblastoma Stem Cells

PIERRE–OLIVIER GUICHET, SOPHIE GUELFI, MARISA TEIGELL, LIESA HOPPE, NORBERT BAKALARA, LUC BAUCHET, HUGUES DUFFAU, KATRIN LAMSZUS, BERNARD ROTHHUT, JEAN–PHILIPPE HUGNOT

STEM CELLS 2015;33:21–34

Presenter: Wan-Ru Liao
Date: 2015/04/16; 15:10-16:00
Commentator: Nan-Shan Chang, PhD
Location: Room 601, Med College

Background: Glioblastoma multiformes (GBMs) are highly vascularized brain tumors with a poor prognosis and characterized by extensive vascularization associated with proliferation of endothelial cells in neurovascular niches. GBMs are heterogeneous tumors containing a subpopulation of multipotent cancer stem cells and these stem cells can differentiate into neuronal, glial, and even vascular cells. In normal vascularization, endothelial cells are covered by pericytes which participate in the regulation of vascular formation, remodeling, stabilization and function. Recent studies have also reported the importance of the Notch pathway in the maintenance and proliferation of GBMs and other cancer stem cells. The Notch pathway is a complex and central regulator of fate and maintenance of embryonic and adult stem cells, but the regulation of angiogenic properties and migration of stem cells is unclear.

Hypothesis: A close link between the Notch1 pathway and the tumoral vascularization process of GBM stem cells.

Results: In the Gb4/Gb7 cultures that isolated from GBMs had multipotentially expression of neural stem cell markers, and generation of glioma-like tumors upon intracranial grafts and generated infiltrative but weakly vascularized tumors in orthotopic grafts. They observed that despite the activation of Notch1 receptor, the typical target proteins (HES5, HEY1, and HEY2) were all less expressed in two GBM stem cells. Ectopic expression of the intracellular form (NICD) to activate Notch1 signaling in these cells that reduced their growth rate and migration was accompanied by a transcriptional switch as the neural stem cell transcription factor expression (ASCL1, OLG2, and SOX2) were downregulated, while HEY1/2, KLF9 and SNAI2 transcription factors were upregulated based on microarray analysis. Loss of OLG2 expression with the reduction in growth was observed after Notch1 stimulation and further examined the reversibility of NICD effects by doxycycline-inducible promoter. Remarkably, NICD expression not only induced the expression of pericyte cell markers (NG2, PDGFRb, and aSMA) but also paralleled with the induction of several angiogenesis-related cytokines (HB-EGF, IL8, and PLGF), matrix metalloproteinases (MMP9), and endothelial cell adhesion proteins (VCAM1, ICAM1, and ITGA9). In contrast to control transplantations, NICD-expressing grafts contained a high number of well-formed vessels with wide lumina lined by characteristic endothelial cells closely associated with GBM cells that undergo transdifferentiation induced by NICD stimulation.

Conclusions: Notch1 stimulation activated an angiogenic program composed of adhesion proteins, cytokines and a metalloprotease. This vascularization switch was associated with pericyte markers driven by GBM stem cell in addition to a sharp reduction in their proliferation and migration rates. Notch1-stimulated GBM stem cells adopted a pericyte like behavior, whereby they closely associated with endothelial cells to generate large regular vessels.

Reference: