Dampak glukosamin terhadap ekspresi gen pluripotensi OCT-4 dan aldh1 sel punca kanker payudara: kajian pensinyalan parakrin terhadap penanda cancer-associated fibroblast stroma = The impact of glucosamine on OCT-4 and aldh1 pluripotent gene expression of breast cancer stem cells: a study of paracrine signaling on stromal cancerassociated fibroblast markers / Fransiscus Nikodemus Hosea

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Abstrak

ABSTRAK
Latar belakang: Cancer stem cells CSC merupakan sel kanker yang memiliki karakteristik sel punca. Kepuncaan CSC berperan dalam menjaga kestabilan jaringan tumor, sifat resisten terhadap terapi dan memicu kejadian relaps. Kepuncaan CSC diduga dapat ditarget secara non-protein specific dengan mengganggu berbagai jalur pensinyalan yang berperan dalam mempertahankan kepuncaan sekaligus menghambat microenvironment. Proses glikosilasi protein berperan dalam kestabilan, transportasi, dan maturasi protein. Glukosamin diduga dapat berpengaruh terhadap interaksi CSC dengan Cancer-associated fibroblast CAF melalui penghambatan glikosilasi. CAF merupakan sel fibroblast di microenvironment yang direkrut oleh sel kanker ke jaringan tumor. Penelitian ini bertujuan untuk menganalisis efek glukosamin terhadap penurunan sifat kepuncaan sel punca kanker payudara ALDH dan hubungannya dengan penanda CAF pada stroma.Metode: Sel punca kanker payudara ALDH ditumbuhkan dalam medium yang mengandung glukosamin selama 24 jam. Conditioned medium yang diperoleh dari sel ALDH CSC-CM atau sel ALDH yang diberi perlakuan glukosamin CSC-CM G digunakan untuk menumbuhkan sel stroma payudara selama 48 jam. Nilai ekspresi gen relatif ALDH1, Oct-4, dan IGF-1 pada CSC, dan gen penanda CAF, ?-SMA dan FAP pada sel stroma diperiksa menggunakan Quantitative Real-Time Polymerase Chain Reaction qPCR .Hasil: Perlakuan glukosamin konsentrasi 4 mM selama 24 jam menyebabkan penurunan ekspresi ALDH1, gen marker CSC pada sel ALDH dan ekspresi Oct-4, gen karakteristik kepuncaan. Ekspresi gen Oct-4 tetap menurun walaupun glukosamin telah dikeluarkan dari medium kultur. Conditioned-medium CM yang diperoleh dari sel punca kanker payudara ALDH dapat memicu peningkatan ekspresi ?-SMA pada sel stroma. Peningkatan ekspresi gen ?-SMA dan FAP pada sel stroma yang diinduksi oleh CSC-CM dapat ditekan oleh CSC-CM G.Kesimpulan: Penghambatan N-glikosilasi oleh glukosamin menyebabkan penurunan ekspresi gen penanda CSC dan gen karakteristik kepuncaan pada sel punca kanker payudara ALDH Perlakuan glukosamin dapat mempengaruhi pensinyalan parakrin CSC-CAF melalui ekspresi gen penanda CAF.
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ABSTRACT
Background Cancer stem cells CSC is known as a subpopulation of cancer cells with stem cell like characteristics. CSC stemness is responsible for tumor maintenance and relapse. A therapeutic agent that is non protein specific yet intensely uptaken by CSC can be a good approach to disrupt the coordinated network in stemness maintenance and simultaneously affect corrupt stromal cells in tumor microenvironment. Glucosamine inhibits post translational glycosylation, essential for sustaining protein

stability, trafficking, and maturation. Cancer associated fibroblast CAF differentiation and recruitment to tumor microenvironment is induced by CSC derived growth factors. This study investigated the effect of glucosamine on stemness in ALDH breast cancer stem cell and its ability to interact with stromal cells.Methods ALDH breast cancer stem cell were cultured in medium containing glucosamine for 24 h. Breast stromal cells were culture in conditioned medium obtained from ALDH cells CSC CM or glucosamine treated ALDH cells CSC CM G . Relative expression of ALDH1, Oct 4, and IGF 1 gene in CSC, and SMA and FAP gene in stromal cells were analyzed using Quantitative Real Time Polymerase Chain Reaction qPCR .Results Upon treatment with 4 mM glucosamine for 24 h, ALDH breast cancer stem cell showed significant decrease in expression of ALDH1, a marker of breast cancer stem cell. Under similar condition, Oct 4 stemness gene was also found to be downregulated. Downregulation of Oct 4 expression was maintained after removal of glucosamine. Stromal cells showed increased expression of SMA myofibroblast marker upon cultured in CSC CM. This upregulation was cancelled in CSC CM G exposed stromal cells.Conclusion N linked glycosylation inhibition by glucosamine results in downregulation of stem cell marker and stem cell gene expression in ALDH breast cancer stem cell. CSC rsquo s stemness influences paracrine interaction between CSC dan CAF via expression of CAF marker in stromal cells