EKSPRESI β CATENIN DAN β4 INTEGRIN PADA KARSINOMA SEL BASAL AGRESIF DAN NON AGRESIF

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ABSTRACT
The expression of β catenin and β4 integrin
In aggressive and non aggressive basal cell carcinoma

Background : Aggressive basal cell carcinoma (BCC) is a high risk type of BCC which frequently locally aggressive and has been associated with greater subclinical depth of extension and a greater rate of local recurrence in BCC with aggressive histopathologic variants. Until now, the role of molecular biology marker in predicting the aggressiveness of BCC is not clear.
Purpose: To determine the expression of β catenin and β4 integrin in the aggressiveness of BCC, to analyze the expression of β catenin and β4 integrin in aggressive BCC compare with non aggressive BCC.
Methods : This research was`done by observational with cross sectional study from 58 primary BCC patients who visited Skin Surgery and Tumor Division Outpatient clinic M Hoesin General Hospital Palembang during periode Januari 2008-December 2009 was involved. Characteristic of the primary BCC patient results were recorded. Skin biopsy from primary BCC lesion were taken and Histopathological examination was performed for detection BCC subtype and Immunohistochemistry test for detection of β catenin and β4 integrin was performed. The level of β catenin and β4 integrin were measured quantitatively. Statistically data were analyzed by using the chi-square, independent sample t test, and multiple logistic regression
Result: The results of this study showed in primary BCC there was a significant correlation between expression of β catenin and β4 integrin in aggressive and non aggressive of BCC ($p < 0,05$), the expression of β catenin ($t = -5006$, $p < 0,05$) and β4 integrin ($t = -3.714$, $p < 0.05$) was significant greater in aggressive than non aggressive of BCC, there was also significant correlation between expression of β catenin and β4 integrin in aggressiveness of BCC (β catenin $p \leq 0.002$, OR=1,154; β4 integrin $p \leq 0.004$, OR=1,067), which means the influence of β catenin has a strong significant 1,154 time and β4 integrin has a strong significant 1,067 time in aggressiveness of BCC.
Conclusion : The expression of β catenin and β4 integrin were significantly greater in aggressive than non aggressive BCC, and there were significant correlation of β catenin and β4 integrin in aggressiveness of BCC with the type of histopathology of BCC based on growth pattern

Key Word: β catenin, β4 integrin, aggressive BCC, non aggressive BCC

RINGKASAN
EKSPRESI β CATENIN DAN β4 INTEGRIN PADA KARSINOMA SEL BASAL AGRESIF DAN NON AGRESIF

Karsinoma sel basal (KSB) agresif adalah KSB risiko tinggi secara umum mudah rekuren setempat/lokal, sedangkan berdasarkan gambaran histopatologi mempunyai hubungan dengan invasi dan infiltrasi ke jaringan sekitarnya secara subklinis dan cenderung rekuren meningkat dengan cepat. Sampai saat ini peranan petanda biologi moleluler dalam memprediksi agresivitas KSB masih belum jelas. Akhir-akhir ini, di era genomik agresifitas KSB terutama dipengaruhi faktor risiko intrinsik berupa disregulasi biologi molekuler. Hampir sebagian besar peneliti berpendapat gambaran histopatologi tipe KSB berdasarkan *growth pattern,* mempunyai hubungan dengan disregulasi biologi molekuler.

Meskipun masih merupakan kontroversi, pada model tikus transgenik KSB berasal dari sel punca epidermis pada *bulge* folikel rambut dan *interfollicular epidermis* (IFE), sehingga diperkirakan KSB merupakan kanker sel punca, yang dalam perkembangannya melalui mekanisme *signal pathway multipel* Wingless (Wnt), dengan β catenin berperan sentral. Pada kanker sel punca epidermis dengan pemeriksaan *DNA labelling retainng cell* (LRC) ternyata ada peningkatan ekpresi β4 integrin.

Penelitian pada KSB primer ternyata agresifitas KSB menunjukkan peralihan epitel normal ke tumor jinak dan ke tumor ganas yang pada perkembangannya melalui mekanisme *signaling pathways multiple genetic*. Dibuktikan pada tikus transgenik KSB sebagai kanker sel punca, perkembangan dan progresifitas diawali dengan fase inisiasi, melalui aktivasi s*ignal pathways complex* Wnt, hipofosforilasi *glycogen synthetase kinase 3 beta* (GSK-3β) menyebabkan β catenin stabil dalam sitoplasma, bertranslokasi ke nukleus, membentuk komplek TCF/LEF - β catenin sebagai faktor transkripsi, *downstream* ke gen target, mengamplikasi sel punca. Pada fase promosi secara biokimia, aktifasi β4 integrin secara langsung dan tidak langsung *crosstalk* dengan *epidermal growth factor* (EGF) mengaktifasi *focal adhesion kinase* (FAK)*, phosphatidylinositol 3kinase* (PI3K). Beta4 integrin *cooperate* β catenin stabil sitoplasma sebagai *maintanance*, fosforilasi *mitogen activated protein kinase* (MAPK)/ *extracelular regulated kinase (ERK)/c-Jun kinase (JNK)* menyebabkan proliferasi sel kanker. Secara biomekanik, fosforilasi *Rac-Rho like GTPasse*, mempromosikan polimerisasi bagian lateral aktin sel kanker dengan pembentukan lamelapodia dan filipodia menyebabkan kontraksi, traksi sitoskeleton-F aktin makin kuat, diikuti kerutan membran basalis, terjadi migrasi dan invasi sel kanker.

Penelitian ini bertujuan menjelaskan ekspresi β catenin dan β4 integrin pada agresifitas KSB, serta menganalisis ekspresi β catenin dan β4 integrin pada KSB agresif dibanding dengan KSB non agresif.

Penelitian ini merupakan penelitian observasional dengan rancangan *cross sectional study* pada 58 pasien KSB primer di Divisi Tumor/Bedah Kulit Unit Rawat Jalan Kulit dan Kelamin RSUP M Hoesin Palembang periode Januari 2008-Desember 2009. Dilakukan pencatatan karakteristik dan biopsi kulit pasien KSB primer, dilanjutkan pemeriksaan histopatologi untuk mengetahui tipe KSB dan imunohistokimia (IHK) untuk mengetahui ekspresi β catenin dan β4 integrin. Data dianalisis secara statistik

dengan uji *chi-square*, *independent sample t test* dan *multiple logistic regression*, (p< 0,05). Secara signifikan ada hubungan distribusi ekspresi β catenin dan β4 integrin pada KSB agresif dan non agresif (p=0,00). Secara signifikan ekspresi β catenin lebih tinggi pada KSB agresif (44.06 ± 10.06) dari KSB non agresif (19.16 ±18.25) (t = -5006, p = 0.00). Secara signifikan ekspresi β4 integrin lebih tinggi pada KSB agresif (78.00 ± 38.24) dari KSB non agresif (40.30 ± 32.24) (t = -3.714, p = 0.00) Secara signifikan ekspresi β catenin dan β 4 integrin lebih tinggi pada KSB agresif dibanding non agresif. Ada pengaruh secara signifikan ekspresi β catenin (p ≤ 0.002 OR=1,154) dan β4 integrin (p ≤ 0.004; OR=1,067) terhadap agresifitas KSB, artinya pengaruh β catenin 1.154 lebih kuat, β4 integrin.1,067 lebih kuat terhadap agrsifitas KSB.

Kesimpulan: Ada hubungan secara signifikan distribusi ekspresi β catenin dan β4 integrin pada KSB agresif dan non agresif; secara signifikan ekspresi β catenin dan β4 integrin pada KSB agresif lebih tinggi dibanding pada KSB non agresif; ada pengaruh ekspresi β catenin dan β4 integrin terhadap agresivitas KSB yang mempunyai hubungan dengan gambaran histopatologi tipe KSB berdasarkan *growth pattern*.

Penemuan baru pada penelitian ini adalah ekspresi β catenin dan β4 integrin yang tinggi berperan sentral terhadap agresivitas KSB, yang mempunyai hubungan dengan gambaran histopatologi tipe KSB berdasarkan *growth pattern*. Ekspresi β catenin dan β4 integrin yang tinggi bermanfaat sebagai penunjang diagnostik dalam memprediksi agresivitas KSB. Para praktisi klinis dapat menentukan modalitas pengobatan dan ramalan prognosis.

SUMMARY
THE EXPRESSION OF β CATENIN AND β4 INTEGRIN IN NON AGGRESSIVE AND AGGRESSIVE BCC

Aggressive basal cell carcinoma (BCC) is high risk type of BCC which frequently locally aggressive and has been associated with greater subclinical depth of extension and a greater rate of local recurrence in tumor with aggressive histopathologic variants. Until now, the role of molecular biology marker in predicting the aggressiveness of BCC is not clear. Recently, in era genomic, it was found that aggressiveness of BCC was associated with intrinsic risk factor, as a molecular biology disregulation. Some researchers reported that histopathology examination based on growth pattern had correlation with molecular biology disregulation.

Although it is still a controversy, a study on transgenic mice model showed that BCC was developed from stem cell in bulge hair follicle and interfollicular epidermis (IFE) so that this type of BCC is considered as a stem cell cancer. The mechanism of aggressiveness of stem cell cancer was through signal pathway multiple Wingless (Wnt) which β catenin has a potential role in it mechanism. It was showed by DNA labelling retaining cell (LRC) in a stem cell cancer which showed increased β4 integrin expression. It seemed thatthese tumor require multiple genetic events to transform from normal epithelium to benign neoplasms and these, to malignancy tumor. Until now, the mechanism of aggressiveness of BCC is still controversy. Basal cell carcinoma study in transgenic mice shown that a stem cell cancer showed the aggressiveness of BCC. At the initial stage, the activation of signal pathways complex Wnt, hypophosphorilation GSK-3β, stable cytoplasma β catenin was translocated to nucleus to form TCF/LEF-β catenin

complex as a transcription factor and downstream gen target amplified stem cell. At promotion and progression stage, in biochemistry mechanism, activation of β4 integrin crosstalk with epidermal growth factor (EGF) in direct and indirect ways activated focal adhesion kinase (FAK), phosphatidylinositol three kinase (PI3K). Co-operate with stable cytoplasma β catenin as a maintainance, phosphorilation of mitogen activated protein kinase (MAPK)/extracelular regulated kinase (ERK)/c-Jun kinase(JNK)/Ras which caused proliferation of cancer cells. Biomechanically, phosphorilation of Rac-Rho like GTPasse promotes actin polymerization at the leading edge and thereby the formation of fillipodia and lamellipodia stable and it caused cytoskeleton and F-actin contraction and the generation of traction forces, basement membran ruffled, migration and invasion of cancer cell occurred.

Purpose: The purpose of this study were to explain the expression of β catenin and β4 integrin in aggressiveness of BCC, and to analyze the expression of β catenin and β4 integrin which is greater in aggressive BCC compare with non aggressive BCC.

Methods: This reseach was done by cross sectional study from 58 primary BCC patients visited skin surgery/Tumor division Outpatient clinic M Hoesin General Hospital Palembang during periode Januari 2008-December 2009. Characteristic of patients with primary BCC were recorded. Skin biopsy from primary BCC lesion were taken and Histopathological examination for detection BCC subtype and Immunohistochemistry test for detection of β catenin and β4 integrin were performed. The level of β catenin and β4 integrin was measured quantitatively. Statistically data were analyzed by using the chi-square, independent sample t test, and multiple logistic regression.

Results: The results of this study showed that there was a significant correlation between primary BCC with expression of β catenin and β4 integrin in aggressive and non aggressive of BCC ($p< 0,05$), the expression of β catenin ($t = -5006$, $p < 0,05$) and β4 integrin ($t = -3.714$, $p < 0.05$) was greater significantly in aggressive BCC than non aggressive of BCC, and there was significant correlation between expression of β catenin and β4 integrin in aggressiveness of BCC (β catenin $p \leq 0.002$, OR=1,154; β4 integrin $p \leq 0.004$, OR=1,067) in aggressiveness of BCC, which means the influence of β catenin has a strong significant 1,154 time and β4 integrin has a strong significant 1,067 time in aggressiveness of BCC.

Conclusions : The expression of β catenin and β4 integrin were significantly greater in aggressive than non aggressive BCC, and there were significant correlation of β catenin and β4 integrin in aggressiveness of BCC with the type of histopathology of BCC based on growth pattern

The new finding in this study indicated that the increase of expression of β catenin and β4 integrin has an central role in aggressiveness of BCC, both of them has correlation with the type of histopathology BCC based on growth pattern. The increasing expression of β catenin and β4 integrin can be used to predict aggressiveness of BCC to support diagnosis of BCC and clinical practitioners can be used to determine modality treatment and prognosis prediction.