DISERTASI

EKSPRESI, MUTASI, METILASI DNA *PHOSPHATASE AND TENSIN HOMOLOG* (PTEN) DAN EKSPRESI *PHOSPHATIDYLINOSITOL 4,5-BISPHOSPHATE* (PIP2) PADA JARINGAN KELOID :

Studi Komparasi dengan Kulit Normal dan Parut Hipertrofi

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ABSTRAK

EKSPRESI, MUTASI, METILASI DNA *PHOSPHATASE AND TENSIN HOMOLOG* (PTEN) DAN EKSPRESI *PHOSPHATIDYLINOSITOL 4,5-BISPHOSPHATE* (PIP2) PADA JARINGAN KELOID : Studi Komparasi dengan Kulit Normal dan Parut Hipertrofi

Latar Belakang: Keloid dan parut hipertrofi merupakan kelainan fibroproliferatif yang ditandai oleh deposisi matriks ekstraseluler yang berlebihan dan aktivasi fibroblas yang persisten. Keloid menunjukkan pertumbuhan progresif dan tingkat kekambuhan yang tinggi. Aktivasi abnormal jalur sinyal proliferatif, termasuk *PI3K/AKT,* telah dikaitkan dengan pembentukan parut patologis. *PTEN* suatu gen penekan tumor, merupakan regulator negatif utama jalur ini. Penelitian ini bertujuan menganalisis ekspresi mRNA *PTEN*, ekspresi protein PTEN, dan fosfolipid *PIP2* pada jaringan keloid dibandingkan dengan kulit normal dan parut hipertrofi, serta menilai adanya metilasi dan mutasi pada jaringan keloid dibandingkan dengan kulit normal dan parut hipertrofi.
Metode: Studi klinis komparasi ini menganalisis ekspresi mRNA *PTEN* menggunakan *qRT-PCR* dan ekspresi protein PTEN dan fosfolipid *PIP2* menggunakan analisis *Western blot* pada spesimen keloid, parut hipertrofi, dan kulit normal. Penelitian ini juga menganalisis terjadinya metilasi dan mutasi pada spesimen keloid, parut hipertrofi, dan kulit normal
Hasil: Ekspresi mRNA *PTEN* menunjukkan kecenderungan menurun pada jaringan keloid (*fold change* 0,73, dan p = 0,206) dan meningkat pada jaringan parut hipertrofi (*fold change* 1,64, dan p = 0,074) tanpa signifikansi dibandingkan kulit normal. Analisis *Western blot* menunjukkan kecenderungan peningkatan kadar protein PTEN (1,02) pada keloid maupun parut hipertrofi (0,93) relatif terhadap kulit normal (0,79), namun perbedaan ini tidak bermakna secara statistik. Sebaliknya Analisis *Western blot PIP2* ekspresi protein cenderung menurun tanpa signifikasi dibandingkan kulit normal. Penelitian ini menemukan terdapat perubahan nukleotida pada *cDNA PTEN* keloid,20%, kulit normal 26,7%, dan parut hipertrofi 33,3% jenis *missense* dengan kategori *varian uncertain significance*. Namun tidak ada perbedaan varian antar kelompok keloid, kulit normal dan parut hipertrofi. Penelitian ini tidak menemukan adanya metilasi DNA *PTEN* jaringan keloid, kulit normal dan parut hipertrofi.
Kesimpulan: Terdapat perbedaan bermakna ekspresi mRNA *PTEN* jaringan keloid dibandingkan parut hipertrofi yang mengindikasikan dinamika regulasi yang berbeda antara kedua fenotipe parut patologis. Tidak adanya perbedaan bermakna pada tingkat protein namun ekspresi protein cenderung meningkat pada jaringan keloid dan ekspresi protein parut hipertrofi cenderung menurun dibanding kulit normal mengindikasikan kemungkinan perbedaan regulasi pasca-transkripsi atau pasca-translasi *PTEN* pada kedua jaringan parut, sedangkan ekspresi *PIP2* cenderung menurun jaringan keloid secara tidak bermakna dan berbeda bermakna pada jaringan parut hipertrofi dibanding kulit normal.

Kata Kunci: *keloid; parut hipertrofi; PTEN; PIP2; jalur PI3K/AKT; ekspresi gen; Western blot; metilasi; mutasi*

ABSTRACT

EXPRESSION, MUTATION, AND DNA METHYLATION OF PHOSPHATASE AND TENSIN HOMOLOG (PTEN) AND PHOSPHATIDYLINOSITOL 4,5-BISPHOSPHATE (PIP2) EXPRESSION IN KELOID TISSUE: A Comparative Study with Normal Skin and Hypertrophic Scars

Background: *Keloids and hypertrophic scars are fibroproliferative disorders characterized by excessive extracellular matrix deposition and persistent fibroblas activation. Keloids demonstrate progressive growth and a high recurrence rate, whereas hypertrophic scars tend to remain confined to the wound area and may undergo spontaneous regression. Aberrant activation of proliferative signaling pathways, including PI3K/AKT, has been implicated in pathological scar formation. PTEN, a tumor suppressor gene, serves as the principal negative regulator of this pathway. However, data regarding PTEN mRNA and protein expression in pathological scar tissue remain limited. This study aimed to analyze PTEN mRNA expression, PTEN protein expression, and PIP2 phospholipid levels in keloid tissue compared with normal skin and hypertrophic scar, as well as to assess the presence of DNA methylation and gene mutation in keloid tissue relative to normal skin and hypertrophic scar.*

Methods: *This comparative clinical study analyzed PTEN mRNA expression using qRT-PCR, and PTEN protein and PIP2 phospholipid expression using Western blot analysis, in keloid, hypertrophic scar, and normal skin specimens. Relative expression levels were compared statistically across groups. DNA methylation and gene mutation were also assessed in all three specimen groups.*

Results: *PTEN mRNA expression showed a tendency toward downregulation in keloid tissue (fold change 0.73; p = 0.206) and upregulation in hypertrophic scar tissue (fold change 1.64; p = 0.074), neither of which reached statistical significance compared with normal skin. Western blot analysis revealed a trend toward higher PTEN protein levels in both keloid (1.02) and hypertrophic scar (0.93) tissue relative to normal skin (0.79); however, these differences were not statistically significant. Conversely, PIP2 protein expression by Western blot tended to be lower in pathological scar tissue, again without reaching statistical significance compared with normal skin. This study identified nucleotide variants in the PTEN cDNA in 20.0% of keloid samples, 26.7% of normal skin samples, and 33.3% of hypertrophic scar samples. All detected variants were missense variants and were classified as variants of uncertain significance (VUS). However, no significant differences in the frequency or distribution of these variants were observed among the keloid, normal skin, and hypertrophic scar groups. This study did not detect PTEN promoter methylation in any of the keloid, normal skin, or hypertrophic scar tissue samples.*

Conclusion: *A statistically significant difference in PTEN mRNA expression was observed between keloid and hypertrophic scar tissue, indicating distinct regulatory dynamics between these two pathological scar phenotypes. The absence of significant differences at the protein level suggests the possibility of*

post-transcriptional or post-translational regulation of PTEN and PIP2 in scar tissue.

Keywords: *keloid; hypertrophic scar; PTEN; PIP2; PI3K/AKT pathway; gene expression; Western*