

# Efek mutasi pre s2 virus hepatitis b subgenotipe b3 strain endemik Indonesia terhadap keparahan penyakit hati tinjauan ekspresi dan aktivasi faktor transkripsi nf b = Effect of pre s2 mutation of hepatitis b virus subgenotype b3 the endemic strain in Indonesia on liver disease severity observation on transcription factor nf b expression and activation

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## Abstrak

[<b>ABSTRAK</b><br>

Studi cross sectional pada pasien hepatitis B di Indonesia menunjukkan korelasi mutasi kodon start pre-S2 dengan keparahan penyakit hati. Peran protein-protein HBs pada aktivasi NF- $\kappa$ B sebagai salah satu faktor dalam induksi keparahan penyakit hati. Studi ini dilakukan untuk melihat efek varian mutan HBs virus hepatitis B subgenotipe B3 sebagai strain endemik di Indonesia pada keparahan penyakit hati dilihat dari ekspresi dan aktivasi NF- $\kappa$ B. Gen HBs dari tiga pasien yang membawa tiga varian HBs berbeda diamplifikasi dan diklon dengan plasmid pcDNA3.1, ditransfeksikan dengan metode lipofektamin ke dalam sel Huh7. Nilai ekspresi mRNA dianalisis dengan real-time PCR terhadap mRNA HBs, I $\kappa$ B- $\beta$ , dan NF- $\kappa$ B (p50). Ekspresi I $\kappa$ B- $\beta$  yang diregulasi oleh NF- $\kappa$ B digunakan sebagai parameter untuk aktivasi NF- $\kappa$ B. Diperoleh plasmid ekspresi HBs dengan mutasi kodon start pre-S2, delesi pre-S2 dan wild type VHB subgenotipe B3. Plasmid rekombinan pcDNA HBs dapat mengekspresikan mRNA HBs dan menurun pada 48 hingga 72 jam. Kecuali pada mutan delesi pre-S2 yang stabil hingga 72 jam. Ekspresi protein HBs berdasar ELISA menunjukkan nilai relatif konstan pada HBs wild type, sedangkan pada HBs mutan kodon start dan delesi meningkat pada 72 jam. Aktivasi NF- $\kappa$ B relatif lebih tinggi oleh tipe wild type dibanding mutan kodon start pre-S2 dan delesi pre-S2, sehingga variasi mutasi tidak memberikan pengaruh pada aktivasi NF- $\kappa$ B, meski varian mutan delesi pre-S2 menunjukkan peningkatan aktivasi NF- $\kappa$ B setelah waktu kultur yang lebih lama dibanding HBs wild type dan mutan kodon start pre-S2. Ekspresi NF- $\kappa$ B (p50) dipengaruhi oleh variasi mutasi, ekspresi p50 lebih tinggi pada mutan kodon start pre-S2 dibanding varian HBs lainnya. Keparahannya penyakit hati oleh mutasi kodon start pre-S2 dapat terkait dengan peningkatan ekspresi p50.

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<b>ABSTRACT</b><br>

Cross sectional study on hepatitis B patients in Indonesia showed association of pre-S2 start codon mutation with severity liver disease. Role of HBs proteins on the activation of NF- $\kappa$ B as one of the factor in liver disease progression. This study was to see the effects of different HBs mutant variants of Hepatitis B Virus (HBV) subgenotype B3 as the endemic strain in Indonesia on the expression and activation of NF- $\kappa$ B. HBs genes of three hepatitis B patients were amplified and cloned to pcDNA3.1, and were transfected using lipofectamine into Huh7 cell line. Expressions on mRNA level for HBs, I $\kappa$ B- $\beta$ , and NF- $\kappa$ B (p50) were evaluated using real-time PCR. I $\kappa$ B- $\beta$  expression which is regulated by NF- $\kappa$ B was used as parameter to measure NF- $\kappa$ B activation. Recombinant plasmid for HBs expression with pre-S2 start codon mutation, pre-S2 deletion and wild type of HBV subgenotipe B3

were obtained. All three clones showed high level of mRNA expression which decreased after 48 to 72 hours, except for pre-S2 deletion which was relatively stable up to 72 hours. HBs protein expression detected using ELISA was constant for HBs wild type whilst increased at 72 hours for pre-S2 start codon mutation and pre-S2 deletion. NF- $\kappa$ B activation was higher for HBs wild type compared to the two mutant variants, suggesting no effect of mutation to increment of NF- $\kappa$ B activation, however pre-S2 deletion mutant showed higher NF- $\kappa$ B activation after longer period of incubation. NF- $\kappa$ B (p50) expression was higher for pre-S2 start codon mutation, suggesting liver disease progression by pre-S2 start codon mutation might associated to increased expression of p50.; Cross sectional study on hepatitis B patients in Indonesia showed association of pre-S2 start codon mutation with severity liver disease. Role of HBs proteins on the activation of NF- $\kappa$ B as one of the factor in liver disease progression. This study was to see the effects of different HBs mutant variants of Hepatitis B Virus (HBV) subgenotype B3 as the endemic strain in Indonesia on the expression and activation of NF- $\kappa$ B. HBs genes of three hepatitis B patients were amplified and cloned to pcDNA3.1, and were transfected using lipofectamine into Huh7 cell line. Expressions on mRNA level for HBs, I $\kappa$ B- $\beta$ ; and NF- $\kappa$ B (p50) were evaluated using real-time PCR. I $\kappa$ B- $\beta$  expression which is regulated by NF- $\kappa$ B was used as parameter to measure NF- $\kappa$ B activation. Recombinant plasmid for HBs expression with pre-S2 start codon mutation, pre-S2 deletion and wild type of HBV subgenotype B3 were obtained. All three clones showed high level of mRNA expression which decreased after 48 to 72 hours, except for pre-S2 deletion which was relatively stable up to 72 hours. HBs protein expression detected using ELISA was constant for HBs wild type whilst increased at 72 hours for pre-S2 start codon mutation and pre-S2 deletion. NF- $\kappa$ B activation was higher for HBs wild type compared to the two mutant variants, suggesting no effect of mutation to increment of NF- $\kappa$ B activation, however pre-S2 deletion mutant showed higher NF- $\kappa$ B activation after longer period of incubation. NF- $\kappa$ B (p50) expression was higher for pre-S2 start codon mutation, suggesting liver disease progression by pre-S2 start codon mutation might associated to increased expression of p50.; Cross sectional study on hepatitis B patients in Indonesia showed association of pre-S2 start codon mutation with severity liver disease. Role of HBs proteins on the activation of NF- $\kappa$ B as one of the factor in liver disease progression. This study was to see the effects of different HBs mutant variants of Hepatitis B Virus (HBV) subgenotype B3 as the endemic strain in Indonesia on the expression and activation of NF- $\kappa$ B. HBs genes of three hepatitis B patients were amplified and cloned to pcDNA3.1, and were transfected using lipofectamine into Huh7 cell line. Expressions on mRNA level for HBs, I $\kappa$ B- $\beta$ ; and NF- $\kappa$ B (p50) were evaluated using real-time PCR. I $\kappa$ B- $\beta$  expression which is regulated by NF- $\kappa$ B was used as parameter to measure NF- $\kappa$ B activation. Recombinant plasmid for HBs expression with pre-S2 start codon mutation, pre-S2 deletion and wild type of HBV subgenotype B3 were obtained. All three clones showed high level of mRNA expression which decreased after 48 to 72 hours, except for pre-S2 deletion which was relatively stable up to 72 hours. HBs protein expression detected using ELISA was constant for HBs wild type whilst increased at 72 hours for pre-S2 start codon mutation and pre-S2 deletion. NF- $\kappa$ B activation was higher for HBs wild type compared to the two mutant variants, suggesting no effect of mutation to increment of NF- $\kappa$ B activation, however pre-S2 deletion mutant showed higher NF- $\kappa$ B activation after longer period of incubation. NF- $\kappa$ B (p50) expression was higher for pre-S2 start codon mutation, suggesting liver disease progression by pre-S2 start codon mutation might associated to increased expression of p50., Cross sectional study on hepatitis B patients in Indonesia showed association of pre-S2 start codon mutation with

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