

Peran Penghambat Matriks Metaloproteinase-9 pada Replikasi Virus Hepatitis B: Kajian terhadap MMP-9, IFNAR1, IFN-, HBsAg, DNA VHB, dan cccDNA, Studi In Vitro pada Hepatosit Tupaia Javanica dan PBMC Manusia = The Role of Matrix Metalloproteinase-9 Inhibitor in Hepatitis B Virus Replication: Analysis of MMP-9, IFNAR1, IFN- \hat{I}^2 , HBsAg, HBV DNA, and cccDNA, an In Vitro Study in Tupaia javanica Hepatocyte and Human PBMC

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Abstrak

Infeksi virus hepatitis B (VHB) merupakan masalah kesehatan global. Terapi yang ada saat ini hanya berdampak minimal terhadap covalently closed circular deoxyribonucleic acid (cccDNA), sehingga eradikasi sulit dicapai. Matriks Metaloproteinase-9 (MMP-9) berperan dalam meningkatkan replikasi VHB, namun belum ada penelitian yang mengevaluasi peran penghambat MMP-9 terhadap replikasi VHB. Kultur primer hepatosit diperoleh dari Tupaia javanica dan diinfeksi dengan VHB manusia, kemudian dibagi menjadi dua kelompok, yaitu kontrol dan intervensi. Kelompok intervensi diberikan penghambat MMP-9 dosis 1 nM, 3 nM, dan 7 nM. Peripheral blood mononuclear cells (PBMC) manusia diperoleh dari pasien hepatitis B kronik, kemudian dibagi menjadi dua kelompok, yaitu kontrol dan intervensi. Kelompok intervensi diberikan penghambat MMP-9 dosis 3 nM. Dilakukan pengukuran HBsAg, DNA VHB, cccDNA, MMP-9, type-1 IFN receptor 1 (IFNAR1), dan interferon- (IFN-) sebelum dan 72 jam setelah pemberian intervensi pada kedua kelompok. Pada kultur primer hepatosit *T. javanica* yang diinfeksi VHB manusia, pemberian penghambat MMP-9 dosis 1 nM, 3 nM, dan 7 nM secara konsisten menurunkan kadar HBsAg, DNA VHB, cccDNA, dan MMP-9. Dosis 3 nM meningkatkan kadar IFNAR1, sedangkan dosis 7 nM meningkatkan kadar IFN-. Dosis 3 nM menunjukkan efek yang lebih optimal dibandingkan dosis lainnya. Pada PBMC manusia dengan infeksi VHB, pemberian penghambat MMP- 9 dosis 3 nM menurunkan kadar HBsAg, DNA VHB, cccDNA, dan MMP- 9, serta meningkatkan kadar IFN-, namun menurunkan kadar IFNAR1. Studi ini menunjukkan bahwa pemberian penghambat MMP-9 dapat menurunkan kadar HBsAg, DNA VHB, cccDNA, dan MMP-9, serta meningkatkan kadar IFN- pada kultur primer hepatosit *T. javanica* dan PBMC manusia.

.....Hepatitis B virus (HBV) infection remains a significant global health concern. Current therapies have minimal impact on covalently closed circular deoxyribonucleic acid (cccDNA), making HBV eradication difficult. Matrix Metalloproteinase-9 (MMP-9) enhance HBV replication, but its inhibition has not been studied. Primary hepatocyte cultures were obtained from *Tupaia javanica* and infected with human HBV, then divided into control and intervention groups. The intervention groups were treated with MMP-9 inhibitors at doses of 1 nM, 3 nM, and 7 nM. Human peripheral blood mononuclear cells (PBMC) were isolated from chronic hepatitis B patients and divided into control and intervention groups. The intervention groups received MMP-9 inhibitors at dose of 3 nM. Measurements of HBsAg, HBV DNA, cccDNA, MMP-9, type-1 IFN receptor 1 (IFNAR1), and interferon- (IFN-) were performed before and 72 hours after intervention in both groups. In *T. javanica* primary hepatocyte culture infected with human HBV, MMP-9 inhibitors at doses of 1 nM, 3 nM, and 7 nM consistently decreased levels of HBsAg, HBV DNA, cccDNA,

and MMP-9. The 3 nM dose increased IFNAR1 levels, while the 7 nM dose increased IFN- levels. The 3 nM dose demonstrated the most optimal effects. In human PBMC with HBV infection, MMP-9 inhibitor at dose of 3 nM decreased levels of HBsAg, HBV DNA, cccDNA, MMP-9, increased IFN- levels, but reduced IFNAR1 levels. This study shows that administration of MMP-9 inhibitors reduced levels of HBsAg, HBV DNA, cccDNA, and MMP-9, while increased IFN- levels in *T. javanica* primary hepatocyte cultures and human PBMC.