

Efek Anti Penuaan Sel Punca Mesenkimal Korda Umbilikalis Manusia: Tinjauan Seluler, Biokimia, dan Organismal pada Tikus Tua = Umbilical Cord Mesenchymal Stem Cells as Anti-Ageing: Cellular, Biochemistry, and Organismal Study in Aged Rats

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Abstrak

Latar belakang: Penuaan merupakan proses yang kompleks, antara lain ditandai oleh deplesi sel punca dan inflamasi kronis. Oleh karena itu, pemberian sel punca mesenkimal (SPM) eksogen tampak menjanjikan untuk mencegah atau mengatasi proses penuaan. SPM diketahui mempunyai kemampuan imunomodulasi, memicu regenerasi, dan dapat berdiferensiasi. Penelitian ini bertujuan untuk mengetahui efek pemberian SPM Korda Umbilikalis Manusia (SPM-KUM) pada tikus tua. Metode: Penelitian ini dilakukan pada tahun 2016-2020 di Fakultas Kedokteran Universitas Indonesia dan Fakultas Kedokteran Hewan Institut Pertanian Bogor. Eksperimen dilakukan pada tikus Sprague-Dawley tua betina dan jantan berumur 22-24 bulan. Tikus tua dibagi menjadi dua kelompok, kontrol dan perlakuan. Kelompok perlakuan terdiri dari dua kelompok dosis SPM-KUM yaitu 106 /kg BB (A) dan 107 /kg BB (B). SPM-KUM diberikan secara intravena selama satu tahun dengan interval 3 bulan sedangkan kelompok kontrol diberikan NaCl 0.9%. Efek SPM-KUM pada penuaan dilihat dari kesintasan, berat badan, performa rotarod, parameter stress oksidatif (MDA dan DNA adduct), parameter inflamasi (IL-6 dan TNF-), telomer, hormon reproduksi (estradiol dan testosteron), dan gambaran histopatologi organ hati dan ginjal. Ekspresi antibodi anti-human juga diperiksa untuk konfirmasi diferensiasi SPM-KUM di jaringan. Di akhir penelitian, tikus muda usia 3-4 bulan digunakan sebagai pembanding. Hasil: Setelah satu tahun, tikus tua mengalami kematian, pemendekan telomer, penurunan performa rotarod, peningkatan kadar MDA, DNA adduct, IL-6 dan TNF-, peningkatan sel Kupffer di hati serta peningkatan ekspresi lipofuscin, infiltrat inflamasi, dan p53 di hati dan ginjal. Pemberian SPM-KUM pada tikus tua memperbaiki kesintasan terutama pada tikus betina yang diberikan dosis 107 /kg BB. Kelompok tersebut memiliki telomer lebih panjang, performa rotarod lebih baik, IL-6 menurun, dan TNF- menurun. Pemberian SPM-KUM juga meningkatkan jumlah sel Kupffer di hati dan mengurangi ekspresi lipofuscin di ginjal tanpa mempengaruhi inflamasi dan ekspresi p53 di hati dan ginjal akibat penuaan. Tidak ditemukan ekspresi antibodi terhadap mitokondria manusia di jaringan hati dan ginjal tikus. Kesimpulan: Pemberian SPM-KUM dapat mencegah proses penuaan dengan mempertahankan panjang telomer, menurunkan sitokin pro inflamasi, memperbaiki performa fisik, mengurangi ekspresi lipofuscin terutama di ginjal sehingga memperbaiki kesintasan. Seluruh efek tersebut terutama karena efek parakrin SPM. Kata kunci: Penuaan, SPM-KUM, Telomer, Sel Kupffer, IL-6, TNF-, Lipofuscin

.....Introduction: Ageing is a complex process, which is marked by stem cell depletion and chronic inflammation as the main findings. Therefore, exogenous mesenchymal stem cells (MSC) administration appears to be a promising therapy for preventing or overcoming the ageing process. Furthermore, MSC is known for its immunomodulatory activity, regenerative ability, and differentiation. The present study is aimed to evaluate the effect of human umbilical cord MSC (hUCMSC) on aged rats. Methods: The study was conducted during 2016-2020 at Faculty of Medicine Universitas Indonesia and Faculty of Veterinary Medicine Bogor Agricultural University. The experiment was conducted on female and male Sprague-

Dawley rats of 22-24 months old. Aged rats were divided into control and hUCMSC-treated groups. The hUCMSC treated groups were divided into two subgroups that received two doses of hUCMSC intravenously, i.e., 106 /kg BW (A) and 107 /kg BW (B), four times a year within three months interval. The control group received normal saline injection. The hUCMSC effect on ageing was evaluated by means of survival, body weight, rotarod performance, oxidative stress parameters (MDA and DNA adduct), pro-inflammatory parameters (IL 6 and TNF-), telomeres, reproductive hormones (estradiol and testosterone), and histopathological features of liver and kidneys. Anti-human antibodies were also detected to confirm the differentiation of hUCMSC in tissues. At the end of the study, young rats of 3-4 months old were sacrificed as a comparison. Results: The administration of hUCMSC 107 /kg BB in aged rats could improve survival, especially in female aged rats. This female group had the longest mean telomere length, improved rotarod performance, decreased IL-6 and TNF-. hUCMSC increased Kupffer cells in liver and reduced lipofuscin expression in kidney without further effect on tissue inflammation and p53 expression. In addition, there was no anti-human mitochondria antibody expression in tissue. Conclusion: hUCMSC could inhibit the ageing process through telomere length maintenance, pro-inflammatory cytokine suppression, physical performance improvement, followed by increased survival. Those effects were mainly through the paracrine effect of the MSC. Keywords: Ageing, hUCMSC, IL-6, Kupffer cell, Lipofuscin, Telomere, TNF-