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Therapy of Rat Bone Marrow Mesenchymal Stem Cell (RBM-MSC) at White *Rattusnorvegicus* Induced Carbon Black against VEGF Expression

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Abstract

This study aims to prove the effectiveness of RBM-MSC therapy to reduce the expression of *Vascular Hndhotel Cvovth Factov* in carbon black-induced white *Rattus novvegicus*. This study used 48 female rats divided into 2 treatment groups with different ages pregnancy in 8 replications. This study was induced with a carbon black dose of 532mg/m^{3}and treated with RBM-MSC dose 1x10^{6}cells/0.1ml intravenously. The results of the study of induction of carbon black at days 6-11 and days 6-1F showed differences in the VECF expression between the control and treatment groups. The conclusion of this study has not been able to reduce the expression of VECF, because shorter times optimally for RBM-MSC.

Key word : Carbon black, (VECF), (RBM-MSC) — rat.

Carbon black was one of the particulate matter which contaminates the environment with blackish color and could permiate through the *placental* barrier which is cytotoxic, teratogenic and triggers inflammation (Carza *et al.*, 2008; Wampler, 2005). VECF plays a role in the formation of *vascular* tissue in the development of the corpus luteum, regeneration of endometrium and aids wound healing especially during the granulation phase (Devries *et al.*, 1992). In teratogenic cases, administration RBM-MSC will possibly suppress the inflammation, apoptosis and congenital defects (Lee *et al.*, 200F).

Materials and Methods

A total of 48 pregnant female rats were divided into six treatment groups. The experimental animals were sacrified according to ethic clarity. Identification of VECF expression by immunohistochemistry by determining VECF was done as per (Buchwalow and Bocker, 2010) which can be seen the number of brownish discoloration compared to controls. The data obtained were analyzed in non-parametric and parametric analytics.

Results and Discussion

VECF is a proangiogenic glycoprotein which functions to increase proliferation, migration, survival of endothelial cells and increase capillary permeability. VECF acts as a pro-inflammatory cytokine by increasing the permeability of endothelial cells, stimulating the expression of endothelial molecular adhesion which is

Table I. The experimental design is presented.

Treatment	P1 Gestational period 6-11 days			P2 Gestational period 6-17 days		
	1(C-)	2(C+)	3	1(C-)	2(C+)	3
a) Carbon black @ 532 mg/m3 / 4h	-	+	+	-	+	+
b) RBM-MSC @ 1 x 10^6 / 0.1 ml IV	-	-	+	-	-	+

(C- Negative Control; C+ Positive Control)

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Table II. Average and Standard Deviafion of wcl= Expressions in the finite Rab Placenta (Rattus n•rve9ieue) Exposed toCarbon Blacfi.

Treatment	ExpressionVEGF X± SD
P1.1	1.75[c] ± 0.707
P1.2	0.50[a] ± 0.926
P1.3	1.63[bc] ± 0.744
P2.1	2.63[c] ± 1.506
P2.2	0.63[ab] ± 1.188
P2.3	2.25[c] ± 0.886

Supeañps W6#e,ennoMdonsd#nsignñoefly (p <u.u5).

having the ability to act as a monocyte chemo attractant. VEGF is expressed by epidermal keratinocytes for healing, increased microvascular permeability and angiogenesis (Werner and Grose, 2003).

The results of the VEGF expression study, with the induction of carbon black at a dose of 532 mg / m^3 at the gestational age of the week 2 compared to the control showed a significant difference in VEGF expression. Similarly, the administration of 532 mg / m^3 of carbon black induction at the third week of gestation also showed significant results compared to controls. Age of pregnancy at week 2 (day 6-11) physiologically normal placenta formed perfectly and also the placental barrier has been formed. This placental line has also functioned optimally in resisting the rate of invasion of foreign agents (in this case carbon black) which enters the placenta through the blood. In addition, this gestational age in rat placenta has a system of blood vessel regeneration and good vascularization. The regeneration and vascularization of the rat placenta is useful to resist invasion of inflammatory agents, due to the type of placenta in mice, which has complex branching in the labyrinthine region of the placenta (Watson and Cross, 2005). When the inducted carbon black enters the placenta and causes inflammation in the placenta through the vascular system, the Hofbauer cell physiological response occurs to phagocytose the carbon black. In addition, *Hofbauer* cells secrete pro-inflammatory VEGF which trigger regeneration of vascular system during the second week of pregnancy (Seval *et al*, 2007).

At three weelcs a{ pregztaztcy (days 6-17) physiologically there is an increase in VEGF expression because, before parturition, trophoblast cells undergoes apoptosis, decreases the ability of placental barrier and remodeling factors of the placental vascularization system. Apoptosis of placental trophoblast cells increases with the presence of foreign agents which are the inflammatory factors due to carbon black entering through blood vessels, resulting in an increase in VEGF expression compared to controls. Whereas the results of the study on the treatment of induction of carbon black at a dose of 532 mg / m^3 treated with RBM-MSC at the second week of gestation did not show a significant difference in VEGF expression compared to the treatment which was only induced with carbon black at a dose of 532 mg / m^3. Similarly, the administration of 532 mg / m^3 of carbon black induction treated with RBM-MSC at the third week of gestation also showed results that were not significantly different compared to the treatment which was only induced with a carbon black dose of 532 mg / m^3. This indicates that the administration of RBM-MSC therapy which was carried out once with a dose of $1x10^6$ cells / 0.1 ml on the 11 and 17 days which then the next day sacrificed and surgery performed less significant in inhibiting the formation of VEGF by cells. The immunosuppressant properties of RBM-MSC against Hofbauer cells which inhibit the formation of FGF and VEGF are known to be the driving force of angiogenesis (Devries *et al*., *loc. cit*).

In inhibiting VEGF formation was carried out by administering doses of RBM-MSC at 2 x 10^6 RBM-MSC cells which were then surgically performed and prepared on the 14th day after RBM-MSC therapy. Inhibition of excessive inflammatory responses involving Hofbauer response and neutrophils prevent the extension of inflammatory phase. The results of histopathological examination show that angiogenesis has been reduced at day 14. Angiogenesis occurs more quickly so that the vascular and cellular responses take place more rapidly (Devries *et al*., *loc. cit*). RBM-MSC releases a number of proangiogenic factors and proteins which modulates the migration of endothelial cells allowing tissue repair. RBM-MSC causes endogenous cell proliferation, stimulates angiogenesis, inhibits the

inRammafory esponse andimmuneresponse, as well as, reduces apoptosis further. RBM-MSC is also accomplishes the stimulation of VEGF, HGF, G-SCF, which play a role in the healing process of injury (Martin, 2005).

Based on the results of this study, the impact of RBM-MSC therapy on suppressing the inflammatory response, necrosis and apoptosis effects of induction of carbon black on the placenta at a dose of $1x10^6$ cells / 0.1 ml has not been seen so that RBM-MSC therapy needs to be done before exposure (as preventive therapy) and takes more than 14 days after administration of therapy to get optimal results.

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