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The Effect of Topical Gel Secretome Hypoxia Mesenchymal Stem Cells (SH-MSCs) on TGF-B and IL-6 Gene Expression in Wistar Rats Excision Wound Models

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ABSTRACT: Wounds on the skin result in damage to the epithelial tissue and skin structure, hampering wound healing and causing acute wounds to become chronic. Secretome Hypoxia Mesenchymal Stem Cells are capable of secretes cytokines and growth factors, including TGF-β which are useful for wound healing. IL-6 is a pro-inflammatory cytokine that is produced in infectious lesions and is also important in wound closure. The aim of the research was to prove the effect of topical SH-MSCs gel on TGF-β and IL-6 gene expression in male Wistar rats with an excision wound model. This study aims to prove the effect of topical gel administration secretome Hypoxia Mesenchymal Stem Cell (SH-MSCs) on TGF-β and IL-6 gene expression in male Wistar rats with an excision wound model. This study is Experimental research with Post-test Only Control Group Design. The number of samples was 18 male Wistar rats with the excision wound model divided into three groups, Group I (K-) was given a basic gel placebo, Group 2 (K+) was given a Clobetasol dose of 0.25g/kg, and Group 3 (P1) was given SH-MSCs gel at a dose of 400 µl/kg BW, treatment for 5 days, on day 6 the skin tissue was examined by RT-PCR to see the expression of the TGF-β and IL-6 genes analyzed by One Way Anova test, continued by Post Hoc LSD test. The average TGF-β gene expression in the P1 group was the highest (1.38) and the mean IL-6 gene expression in the P1 group was the lowest (0.72). One Way Anova test result showed a significant difference in TGF-β gene expression with a value of p=0.056 (p<0.05) and IL-6 p=0.47 (p<0.05). Post Hoc LSD test result on TGF-β gene expression shows that administration of 400µl/kg BW SH-MSCs can increase TGF-β gene expression and reduce IL-6 expression in Wistar rats with an excision wound model. The administration of topical gel SH-MSCs dose of 400 µl/kg BW was proven to significantly increase TGF-β levels in male Wistar rat excision wound model. The administration of topical SH MSCs dose of 400 µl/kg BW can reduce IL-6 levels in male Wistar rat excision wound models.

KEYWORDS: SH-MSCs, hypoxia, TGF-β, IL-6, excision wounds

I. INTRODUCTION

Wounds that occur on the skin result in damage to the epithelial tissue and skin structure.[1] Wound healing is hampered and scar tissue forms.2 If an acute wound develops into a chronic condition, it can reduce the aesthetics of the skin, and the patient will bear the burden of therapy costs which are not cheap.[2] Wound healing that gets a lot of attention is using Mesenchymal Stem Cells (MSC), because they have the ability to differentiate and secrete cytokines and growth factors, including Transforming Growth Factor beta (TGF-β) which is useful for wound healing.[2] Culture with hypoxic environmental conditions increases the quality of MSCs in terms of proliferation, and survival ability, and secretes more cytokines and growth factors.[3] TGF-β is a central growth factor that has a role at each stage of wound healing, especially in the inflammation and proliferation phases.[4]

TGF-β is a powerful anti-inflammatory cytokine in regulating uncontrolled inflammation.[5] The combination of TGF-β and IL-6 is required for Th17 differentiation of CD4 T cells+ naive, by encouraging the development of naïve CD4 T cells+, IL-6 plays an important role in bridging the gap between innate and acquired immune responses.[6] Therapy secretome as a promising approach in overcoming tissue and organ regeneration.[7] Preconditioning culture in a hypoxic environment is a procedure to improve the quality of MSCs.3 In wound healing, roles of secretome MSC hypoxia using a topical gel have been shown to be more effective.[8] The effect of giving secretome MSC hypoxia in wound healing requires further research.

The Effect of Topical Gel Secretome Hypoxia Mesenchymal Stem Cells (SH-MSCs) on TGF-B and IL-6 Gene Expression in Wistar Rats Excision Wound Models

Wounds are a widespread medical problem that affects people everywhere in the world. In the United States, approximately 11 million people suffer from it, and each year, 300,000 people are hospitalized.[9] Acute and chronic wounds occur more frequently each year. The number of people experiencing injuries increased from 7.5% in 2012 to 8.2% in 2013, according to Riskesdas Indonesia, with acute injuries accounting for the majority of cases.[10] Wound healing stages are generally disrupted, including acute wounds and chronic wounds, due to prolonged inflammation which inhibits wound healing by preventing it from progressing through the proliferative phase, which causes the wound to become chronic.[11] These chronic, prolonged wounds require special treatment at a significant cost.[12]According to research using topical subcutaneous injection of MSC-CM, compared with topical gel MSC-CM worked better on day 6, it was found that the topical group had significantly higher levels of PDGF and fibroblast density on day 6 of wound healing.[8] MSCs can also reduce inflammation, and burn scar formation, and have been shown in preclinical trials to accelerate the healing of acute burn wounds.[13] Other studies at TNF-α concentrations of 5 and 10 ng/mL significantly increased TGF-β and IL-10 levels. In addition, TGF-β and IL-10 levels were significantly inversely correlated with each other with TNF-α at doses of 5 and 10 ng/mL in suppressive inflammation.[5] Although the function of MSCs in the re-epithelialization process has shown promising results including well-organized epidermal regeneration and good quality of re-epithelialization, the question of the efficacy of MSCs in cell therapy remains to be resolved.[14]

MSCs in hypoxic conditions have proven to be more effective in reducing inflammation and accelerating wound healing.[15,16] Release more cytokines and growth factors.[17] The main growth factor is the TGF-β factor, important for every step of wound healing in the inflammatory and proliferative phases.[18] Through its isoforms, TGF-β increases migration and activation of inflammatory cells during the inflammatory phase of wound healing and controls re-epithelialization, angiogenesis, and granulation tissue development during the proliferative phase.[19] On the other hand, hypoxia-conditioned MSCs reduce inflammation by blocking the NF-kβ pathway and secreting anti-inflammatory cytokines.[20]

Proinflammatory cytokines such as IL-6, IL-1, and TNF-a released as a result of the NF-kβ-mediated inflammatory response cause skin inflammation.[21,22] The cytokine IL-6 plays an important role in the wound healing process.[23] Controlled inflammation is associated with faster wound healing rates.[24] Hypoxic MSC therapy has the capacity for differentiation, and immunoregulation and has no risk of post-injection rejection.[25] The effect of topical gel Secretome Hypoxia MSCs on wound healing in Wistar rats with the excision wound model on the expression of the TGF-β and IL-6 genes requires an in-depth explanation.

II. MATERIAL AND METHOD

This research is in vivo experimental research with Post-Test Only Control Group Design. This study used male Wistar rats as research subjects and were divided into three groups, negative control (K-) is rats with excision wounds treated with basic gel placebo, positive control (K+) is rats with excision wounds treated with Clobetasol dose 0.25g/kg BW, and P1 Group is rats with excision wounds were smeared with topical SH-MSCs gel at a dose of 400µL/kg BW.

III. RESULT

In this study, researchers found that MSCs were able to express CD90 (97.3%), CD29 (97.0%), and slightly expressed CD45 (1.2%) and CD31 (4.8%) (Table 1).

Table 1.

Group	Base gel (K-)	Clobetasol (K+)	SH-MSC 400 µL (P1)	P- value
Mouse 1	0,62	1,41	1,11	
Mouse 2	0,71	0,69	1,31	
Mouse 3	0,39	0,65	1,25	
Mouse 4	0,48	1,10	1,43	
Mouse 5	0,92	0,65	1,68	
Mouse 6	0,61	1,23	1,53	
Mean	0,62	0,95	1,38	
SD	0,19	0,33	0,20	
Shapiro wilk	0,94*	0,15*	0,99*	
Levene test	0,056**			

Normality and homogeneity test of TGF-β gene expression between treatment groups

Information:

**Saphiro Wilk test* (p > 0,05 = normal)

***Levene's Test* (p > 0.05 = homogeneous)

The Effect of SH-MSCs on TGF-β Gene

Expression

Table 1 shows that the average TGF-β gene expression in the P1 group is the highest, followed by the average TGF-β gene expression in the K+ group. Next, the average expression of the TGF-β gene for the K- group. The TGF-β gene expression data for the three groups were all normally distributed, as shown by the Shapiro Wilk test result with the p-value obtained > 0.05, and also had homogeneous data variance as shown in the Levene's test result with the p-value obtained 0.056 (p>0.05). The distribution and variance of TGF-β gene expression data were normal and homogeneous.

Table 2. Post Hoc LSD test result in TGF-β gene expression

Group	Comparison Group	Sig.	95% Confidence Interval	
			Lower limit	Upper limit
K-	K+	0,038*	-0.6357	-0.0199
	P1	0,000*	-1.0703	-0.4545
K+	K-	0,038*	0.0199	0.6357
	P1	0,009*	-0.7425	-0.1267
P1	K-	0,000*	0.4545	1.0703
	K+	0,009*	0.1267	0.7425

* indicates a meaningfully different group.

The Tamhane test result (Table 2) shows that there was a significant difference between the K- with K+ (0.038) and K- with P1 (0.000), K+ with K- (0.038) and K+ with P1 (0.009) has a significant difference as well as in the P1 with K- (0.00) and P1 with K+ obtained a p-value of 0.009 (p <0.05) so that there was a significantly different between the groups. The Post Hoc LSD test result of TGF-β gene expression data shows that the administration of SH-MSCs topical gel dose of 400 µl/kgBB can increase TGF-β gene expression in male Wistar rats excision wound models.

Table 3. Normality and Homogeneity test of IL-6 gene expression between treatment groups

Group	Base gel (K-)	Clobetasol (K+)	SH-MSC 400 µL (P1)	p-value
Mouse 1	2,39	1,31	0,85	
Mouse 2	1,72	1,34	0,30	
Mouse 3	1,86	1,92	0,73	
Mouse 4	2,00	1,46	0,93	
Mouse 5	2,61	1,55	0,93	
Mouse 6	2,00	1,76	0,61	
Mean	2,10	1,56	0,72	
SD	0,34	0,24	0,24	
Shapiro wilk test	0,49*	0,51*	0,24*	
Levene test	0,47*			

Information:

*Saphiro Wilk Test (p > 0,05 = Normal)

** Levene's Test (p > 0.05 = Homogeneous)

Table 3 shows that the average IL-6 gene expression in the K- group has the highest value, followed by the average IL-6 gene expression in the K+ group. Furthermore, the lowest mean IL-6 gene expression was in the P1 group. The IL-6 gene expression data for the three groups were all normally distributed, as shown by the Shapiro Wilk test obtained a p-value of > 0.05, and also had homogeneous data variance as shown in the Levene's test result with a value of p=0.47 (p>0.05). The distribution and variance of IL-6 gene expression data were normal and homogeneous. Statistical analysis using the One Way Anova test obtained a p-value of p=0.000 (p<0.05) so it is stated that there is a significant difference in the average expression of the IL-6 gene between the three groups. One Way Anova test result which is significant is followed by the Post Hoc LSD test to see which groups have the most influence.

Table 4. Post Hoc LSD test result on IL-6 gene expression in each group

Group	Comparison Group	Sig.	95% Confidence Interval	
			Lower limit	Upper limit
K-	K+	0,004*	0.1999	0.8911
	P1	0,000*	1.0300	1.7212
K+	K-	0,004*	-0.8911	-0.1999
	P1	0,000*	0.4845	1.1757
P1	K-	0,000*	-1.7212	-1.0300
	K+	0,000*	-1.1757	-0.4845

*indicates a meaningfully different group.

Post hoc test results (Table 4) show that there is a significant difference in the average of K- and K+ group (0.004), while K- and P1 (0.000) and K+ and K- (0.004) have significant difference, K+ and P1 (0.000), P1 with K- (0.000), and P1 and K+ (0.000), there are significant differences ($p < 0.05$). Post Hoc LSD test result on IL-6 gene expression shows that topical administration of 400 µl/kg BW SH-MSCs gel can reduce IL-6 gene expression in male Wistar rat excision wound models.

V. DISCUSSION

An excision wound is a type of wound that occurs on the surface of the skin where the bottom layer of the skin is cut to varying depths with regular wound edges.[26] Skin wound healing as an important physiological process involves the collaboration of various cell strains and their products. Recovery from lesions caused by local aggression begins early in the inflammatory stage. The repair consisting of the replacement of specific structures is caused by the deposition and regeneration of collagen, corresponding to the process of cell proliferation and differentiation posteriorly through the stem cell network.[27]

The inflammatory phase begins after trauma to the skin and continues for up to five days. This phase is important for hemostasis and preventing bacterial colonization or infection.[28] The initial phase when an injury occurs is the homeostasis phase which involves drainage of the lymphatic and blood systems to stop blood loss. A highly integrated wound-healing cascade is then initiated with the recruitment of proinflammatory cytokines that trigger inflammation and initiate the inflammatory phase.[29]

An important phase of wound healing is the change from the inflammatory phase to the proliferative phase. The inflammatory phase is critical for triggering hemostasis and activating the innate immune system, protecting the body from invasive infections, and assisting in the removal of dead tissue. Prolonged inflammation is associated with severe scarring and may hinder regular wound healing.[30]

The most important phase of the wound healing process is the change from the inflammatory phase to the proliferative phase.[31] Research reports using hypoxia mesenchymal stem cell which was injected around the wound area can speed up wound healing by shortening the transition period from the inflammatory phase to the proliferation phase. Mesenchymal stem cells will migrate to the wound area.[32] This study showed that TGF-β levels in the P1 group by administering 400 µl SH-MSC topical gel increased compared to the K- group.

In line with several studies reported by (Chen et al., 2014), (Widowati et al. 2017), (Peruzzaroet 2019), and (Son et al. 2019). Compared with normoxia MSCs, hypoxia MSCs have a better ability to survive in the wound area. This is caused by the injury microenvironment and hypoxic environment, Hypoxia-induced factor 1 (HIF-1) can increase at oxygen levels between 2-9%, decreasing levels of reactive oxygen species (ROS) in mitochondria and activating nuclear factor kappa B (NFkB). Additionally, HIF-1 promotes the production of Normal Cellular Prion Protein (PrPC). NF-κB and PrPC promote the development of antioxidant enzymes, repairing growth factors, and anti-apoptotic proteins.[33,34] The presence of more IL10 and TGF-b secreted by MSCs as a result of incubation in hypoxia may explain the increased capacity of MSCs to initiate polarization. It is known that MSCs release more cytokines in hypoxic conditions, such as IL10 and TGF-b.[85] This study is in line with other studies that used a 400µl dose of hypoxic MSC secretome gel where there was a reduction in inflammation in peritoneal adhesions.[35]

This study showed that IL-6 levels in the P1 group by administering 400 µl SH-MSC topical gel decreased compared to the K- group, in line with other studies showing that there was a reduction in inflammation through activation of the IL-10 STAT3 pathway. IL-10 will bind to IL-10R resulting in activation of JAK 1 which induces STAT3 phosphorylation. The STAT3 protein will enter the nucleus and activate the SOSC3 mRNA sequence which will then be expressed intracellularly and can suppress the pro-inflammatory signaling pathway, namely NF-κB. Suppression of the NF-κB pathway will cause a decrease in the secretion of pro-inflammatory cytokines, one of which is IL-6.[36]

Other research using UC-MSCs showed that serum levels of IL-6 and TNF-α can be used as predictors to evaluate the development and progression of diabetes. Serum levels of IL-6 and TNF-α were significantly reduced after treatment in DM mice and suggested treatment may improve insulin resistance.[37]

V. CONCLUSION

The Administration of Topical gel secretome hypoxia mesenchymal stem cells (SH-MSCs) at a dose of 400 µL/kg BW was shown to have a significant effect on increasing TGF-β gene expression and reducing IL-6 gene expression in male Wistar rat excision wound models.

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REFERENCES

1) Prastika DD, Setiawan B, Saputro AL, Yudaniayanti IS, Wibawati PA, Fikri F. Effect of topical shrimp chitosan on collagen density in healing excision wounds in white rats.Journal of Veterinary Medicine. 2020;3(1):101. doi:10.20473/jmv.vol3.iss1.2020.101-107
2) Aydemir I, Öztürk Ş, Kılıçaslan Sönmez P, Tuğlu Mİ. Mesenchymal stem cells in skin wound healing.Anatomy. 2016;10(3):228-234. doi:10.2399/ana.16.043
3) Wiredu Ocansey DK, Pei B, Yan Y, et al. Improved therapeutics of modified mesenchymal stem cells: An update. J Transl Med. 2020;18(1). doi:10.1186/s12967-020-02234-x
4) Behm B, Babilas P, Landthaler M, Schreml S. Cytokines, chemokines and growth factors in wound healing. Journal of the European Academy of Dermatology and Venereology. 2012;26(7):812-820. doi:10.1111/j.1468-3083.2011.04415.x
5) Putra A, Ridwan FB, Putridewi AI, et al. The role of tnf-α induced mscs on suppressive inflammation by increasing tgf-β and il-10. Open Access Maced J Med Sci. 2018;6(10):1779-1783. doi:10.3889/oamjms.2018.404
6) Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 cells. Annu Rev Immunol. 2009;27:485-517. doi:10.1146/annurev.immunol.021908.132710
7) Daneshmandi L, Shah S, Jafari T, et al. Emergence of the Stem Cell Secretome in Regenerative Engineering. Trends Biotechnol. 2020;38(12):1373-1384. doi:10.1016/j.tibtech.2020.04.013
8) Kuntardjo N, Dharmana E, Chodidjah C, Nasihun TR, Putra A. TNF-α-Activated MSC-CM Topical Gel Effective in Increasing PDGF Level, Fibroblast Density, and Wound Healing Process Compared to Subcutaneous Injection Combination. Bandung Medical Magazine. 2019;51(1):1-6. doi:10.15395/mkb.v51n1.1479
9) Demidova-Rice TN, Hamblin MR, Herman IM. Acute and impaired wound healing: Pathophysiology and current methods for drug delivery, part 1: Normal and chronic wounds: Biology, causes, and approaches to care. Adv Skin Wound Care. 2012;25(7):304-314. doi:10.1097/01.ASW.0000416006.55218.d0
10) Pakaya D. The role of Vitamin C on the skin. Medika Tadulako: Medical Scientific Journal, Faculty of Medicine and Health Sciences. Published online 2014.
11) Desai S, Jagtap J, Sainani S, Bhonde R. Guiding stem cells for cutaneous repair.Current Research in Pharmacology and Drug Discovery. 2023;4. doi:10.1016/j.crphar.2022.100145
12) Murphy PS, Evans GRD. Advances in Wound Healing: A Review of Current Wound Healing Products. Plast Surg Int. 2012;2012:1-8. doi:10.1155/2012/190436
13) Rangatchew F, Vester-Glowinski P, Rasmussen BS, et al. Mesenchymal stem cell therapy of acute thermal burns: A systematic review of the effect on inflammation and wound healing. Burns. 2021;47(2):270-294. doi:10.1016/j.burns.2020.04.012
14) Chen D, Hao H, Fu X, Han W. Insight into reepithelialization: How do mesenchymal stem cells perform? Stem Cells Int. 2016;2016. doi:10.1155/2016/6120173
15) Jeschke MG, Rehou S, McCann MR, Shahrokhi S. Allogeneic mesenchymal stem cells for treatment of severe burn injury. Stem Cell Res Ther. 2019;10(1). doi:10.1186/s13287-019-1465-9
16) Lotfinia M, Lak S, Ghahhari NM, et al. FULL LENGTH Iranian Hypoxia Pre-Conditioned Embryonic Mesenchymal Stem Cell Secretome Reduces IL-10 Production by Peripheral Blood Mononuclear Cells. Biomed J. 2017;21(1):24-31. doi:10.6091/.21.1.24
17) Trisnadi S, Muhar AM, Putra A, Kustiyah AR. Hypoxia-preconditioned mesenchymal stem cells attenuate peritoneal

adhesion through TGF-β inhibition. Universal Medicine. 2020;39(2):97-104. doi:10.18051/univmed.2020.v39.97-104
18) Behm B, Babilas P, Landthaler M, Schreml S. Cytokines, chemokines and growth factors in wound healing. Journal of the European Academy of Dermatology and Venereology. 2012;26(7):812-820. doi:10.1111/j.1468-3083.2011.04415.x
19) Gilbert RWD, Vickaryous MK, Viloria-Petit AM. Signalling by transforming growth factor beta isoforms in wound healing and tissue regeneration. J Dev Biol. 2016;4(2). doi:10.3390/jdb4020021
20) Su VYF, Lin CS, Hung SC, Yang KY. Mesenchymal stem cell-conditioned medium induces neutrophil apoptosis associated with inhibition of the NF-κb pathway in endotoxin- induced acute lung injury. Int J Mol Sci. 2019;20(9). doi:10.3390/ijms20092208
21) Su CM, Wang L, Yoo D. Activation of NF-κB and induction of proinflammatory cytokine expressions mediated by ORF7a protein of SARS-CoV-2. Sci Rep. 2021;11(1). doi:10.1038/s41598-021-92941-2
22) Bashir MM, Sharma MR, Werth VP. UVB and proinflammatory cytokines synergistically activate TNF-α production in keratinocytes through enhanced gene transcription. Journal of Investigative Dermatology. 2009;129(4):994-1001. doi:10.1038/jid.2008.332
23) Ayu K, Erika A, Mas A, Batari UA, Watampone T.The Effect of Applying Topical Red Dragon Fruit Extract Cream (Hylocereus Polyrhizuz) to Acute Wounds on Interleukin-6 Levels in the Inflammatory Phase in Wistar.; 2018. https://www.researchgate.net/publication/323545270
24) Xiao S, Huang G, Wei Z, et al. IL-10 Gene-modified human amniotic mesenchymal stem cells augment regenerative wound healing by multiple synergistic effects. Stem Cells Int. 2019;2019. doi:10.1155/2019/9158016
25) Jeschke MG, Rehou S, McCann MR, Shahrokhi S. Allogeneic mesenchymal stem cells for treatment of severe burn injury. Stem Cell Res Ther. 2019;10(1). doi:10.1186/s13287-019-1465-9
26) Priyandari Y, Arfina Titi Maulidah Umatjina S.Topical Jatropha Curcas Sap Accelerates the Healing Time of Excision Wounds in Mice (Effect of Jatropha Curcas Topical Increases Wound Healing Excision Period of Mice).
27) Eming SA, Krieg T, Davidson JM. Inflammation in wound repair: Molecular and cellular mechanisms. Journal of Investigative Dermatology. 2007;127(3):514-525. doi:10.1038/sj.jid.5700701
28) Gurtner G, Wong VW. Wound healing: normal and abnormal. Grabb and Smith's plastic surgery. 2007;6:15-22.
29) Widowati W, Rihibiha DD, Khiong K, Widodo MA, Sumitro SB, Bachtiar I. Hypoxia in Mesenchymal Stem Cell. In:Hypoxia and Human Diseases. InTech; 2017. doi:10.5772/65510
30) Yustianingsih V, Sumarawati T, Putra A. Hypoxia enhances self-renewal properties and markers of mesenchymal stem cells. Universal Medicine. 2019;38(3):164-171. doi:10.18051/univmed.2019.v38.164-171
31) Widyaningsih W.Effect of Hypoxic Mesenchymal Stem Cell Secretome Administration on C-Peptide, IL-6 Levels, and Type-2 Macrophage Polarization (In Vivo Experimental Study in Type 2 Diabetes Mellitus Obese Rats) (Doctoral Dissertation, Sultan Agung Islamic University (Indonesia)).; 2022.
32) Putra A, Alif I, Hamra N, et al.MSC-Released TGF-β Regulate α-SMA Expression of Myofibroblast during Wound Healing. Journal of Stem Cells & Regenerative Medicine.; 2020.
33) Xiao S, Huang G, Wei Z, et al. IL-10 Gene-modified human amniotic mesenchymal stem cells augment regenerative wound healing by multiple synergistic effects. Stem Cells Int. 2019;2019. doi:10.1155/2019/9158016
34) Singampalli KL, Balaji S, Wang X, et al. The Role of an IL-10/Hyaluronan Axis in Dermal Wound Healing. Front Cell Dev Biol. 2020;8. doi:10.3389/fcell.2020.00636
35) Muhar AM, Putra A, Warli SM, Munir D. Hypoxia-mesenchymal stem cells inhibit intra-peritoneal adhesions formation by upregulation of the il-10 expression. Open Access Maced J Med Sci. 2019;7(23):3937-3943. doi:10.3889/oamjms.2019.713
36) Pan XH, Huang X, Ruan GP, et al. Umbilical cord mesenchymal stem cells are able to undergo differentiation into functional islet-like cells in type 2 diabetic tree shrews. Mol Cell Probes. 2017;34:1-12. doi:10.1016/j.mcp.2017.04.002