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# 美沙拉嗪对溃疡性结肠炎患者血清 CRP, IL-10 及 TNF- $\alpha$ 水平的影响 \*

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**摘要 目的:**探讨美沙拉嗪对溃疡性结肠炎患者血清 CRP, IL-10 及 TNF- $\alpha$  水平的影响。**方法:**收集我院就诊的 120 例溃疡性结肠炎患者,随机分为实验组和对照组,每组 60 例。两组给予柳氮磺吡啶肠溶片治疗,实验组患者给予美沙拉嗪肠溶片治疗。观察并比较两组患者治疗前后血清 C-反应蛋白(CRP)、肿瘤坏死因子- $\alpha$ (TNF- $\alpha$ )及白介素-10(IL-10)水平、临床疗效及安全性。**结果:**与治疗前相比,治疗后两组患者血清 CRP 及 TNF- $\alpha$  水平均下降,而 IL-10 水平均升高,差异具有统计学意义( $P<0.05$ );与对照组相比,实验组患者血清 CRP 及 TNF- $\alpha$  水平较低,而 IL-10 水平较高,差异具有统计学意义( $P<0.05$ );与对照组相比,实验组患者临床治疗有效率较高,不良反应发生率较低,差异具有统计学意义( $P<0.05$ )。**结论:**美沙拉嗪能够抑制溃疡性结肠炎患者的炎症反应水平,降低 CRP、TNF- $\alpha$  水平,升高 IL-10 水平,临床疗效较好,且用药安全。

**关键词:**美沙拉嗪;溃疡性结肠炎;CRP;IL-10;TNF- $\alpha$

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## Effect of Mesalazine on Serum Levels of CRP, IL-10 and TNF- $\alpha$ in Patients with Ulcerative Colitis\*

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**ABSTRACT Objective:** To investigate the effects of mesalazine on serum levels of CRP, IL-10 and TNF- $\alpha$  in of patients with ulcerative colitis. **Methods:** 120 patients with ulcerative colitis were randomly divided into the experimental group and the control group, with 60 cases in each group. The patients in the control group were treated with sulfasalazine enteric-coated tablets, while the patients in the experimental group were treated with mesalazine enteric-coated tablets. Then serum levels of C- reactive protein (CRP), tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin-10 (IL-10), and clinical efficiency and safety in the two groups were observed and compared before and after the treatment. **Results:** Compared with before treatment, the serum levels of CRP and TNF- $\alpha$  decreased, while the levels of IL-10 increased in the two groups after treatment, and the differences were statistically significant ( $P<0.05$ ); Compared with the control group, the serum levels of CRP and TNF- $\alpha$  were lower, and the IL-10 was higher in experimental group, and the differences were statistically significant ( $P<0.05$ ); Compared with the control group, the clinical effective rate in the experimental group were higher, while the incidence of adverse reactions was lower, and the differences were statistically significant ( $P<0.05$ ). **Conclusion:** Mesalazine can reduce the serum levels of IL-10, CRP and TNF- $\alpha$  in patients with ulcerative colitis, which is effective and safety for clinical treatment.

**Key words:** Mesalazine; Ulcerative colitis; C-reactive protein; Interleukin-10; Tumor necrosis factor alpha

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### 前言

溃疡性结肠炎(ulcerative colitis, UC)是临床常见的慢性肠道非特异性炎症性疾病,患者以腹痛腹泻、黏液脓血便为主要的临床特征<sup>[1]</sup>。病变部位多在结肠多发,直肠以及回肠末端也是其发病部位<sup>[2]</sup>。近年来,溃疡性结肠炎的发病率逐年升高,且其病情连续,反复发作,病程较长,其中,IL-10、TNF- $\alpha$  以及 CRP 等炎症因子均证实溃疡性结肠炎患者血清中水平升高,进而造成组织的炎症损害,破坏肠道黏膜,引起溃疡性结肠炎的发生

<sup>[3]</sup>。美沙拉嗪治疗溃疡性结肠炎能够对患者受损的肠黏膜产生恢复作用,疗效确切,且不良反应较少<sup>[4]</sup>。研究表明<sup>[5]</sup>,美沙拉嗪还能够抑制炎症因子的相关基因的表达,减少其对于粒细胞等的刺激,阻断其合成过程,达到阻止肠道黏膜进一步损害的目的。本实验通过观察溃疡性结肠炎患者血清 CRP, IL-10 及 TNF- $\alpha$  水平的变化,探讨美沙拉嗪对于溃疡性结肠炎的治疗作用,现报道如下。

### 1 资料与方法

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### 1.1 临床资料

收集 2015 年 1 月~2016 年 6 月于我院就诊的 120 例溃疡性结肠炎患者,随机分为两组,每组 60 例。实验组内男性 36 例,女性 24 例,患者平均年龄( $38.36 \pm 0.83$ )岁;对照组内男性 34 例,女性 26 例,患者平均年龄( $47.19 \pm 0.79$ )岁。所有患者均符合《对我国炎症性肠病诊断治疗规范的共识意见》中的相关诊断标准,并经均经电子结肠镜检查确诊。两组患者一般资料相比有可比性( $P>0.05$ )。

### 1.2 纳入标准

患者均符合溃疡性结肠炎的诊断标准。所有入选对象年龄在 25-55 岁之间,性别不限;所有患者均无肠梗阻、肠道出血、感染性结肠癌等疾病;所有患者均无重要器官疾病;患者无肝肾功能不全;患者治疗前未使用过实验相关药物;患者无恶性肿瘤;所有患者均签署知情同意书同意进行实验措施。

### 1.3 排除标准

排除不符合纳入标准的患者,排除年龄在 25 岁以下,55 岁以上的患者;排除妊娠以及哺乳期女性,排除有肠结核、克罗恩病以及其他消化系统疾病的患者;排除有重要器官重大疾病的患者;排除有恶性肿瘤的患者;排除实验前接受过消化道手术的患者;排除实验前已使用过实验药物的患者;排除实验前使用过糖皮质激素、免疫抑制剂的患者;排除不愿接受实验措施的患者。

### 1.4 方法

**1.4.1 治疗方法** 两组患者均给予相应的治疗措施,基础治疗包括给予患者清淡饮食,纠正患者不良的营养状态,忌烟酒以及刺激性食物,纠正患者水电解质以及酸碱平衡失常。对照组患者在此基础上给予柳氮磺吡啶肠溶片(国药准字 H31020840 上海福达制药有限公司)2 g/次,4 次/d,饭前口服;实验组患者给予美沙拉嗪肠溶片(国药准字 H19980148 葵花药业集团佳木斯鹿灵制药有限公司)1 g/次,3 次/d,饭前口服。治疗 4 周

为 1 个疗程,连续两个疗程。在治疗期间根据患者情况及时调整药量。

**1.4.2 C-反应蛋白(CRP)水平检测** 所有患者治疗前后取外周静脉血 3 mL,采用免疫透射比浊法检测患者血清 C-反应蛋白(CRP)水平。

**1.4.3 肿瘤坏死因子- $\alpha$ (TNF- $\alpha$ )、白介素-10(IL-10)水平检测** 所有患者治疗前后采集外周静脉血 5 mL,离心取上清,采用 ELISA 法检测患者肿瘤坏死因子- $\alpha$ (TNF- $\alpha$ )、白介素-10(IL-10)水平。

**1.4.4 临床疗效评价** 治疗后所有患者的临床疗效进行评价,患者治疗后临床症状或体征消失,每日大便次数低于 2 次,便常规检查未见红、白细胞,经肠镜检查,患者肠道黏膜正常为显效;患者治疗后临床症及状体征好转,每日大便次数在 2~4 次之间,便常规检查,患者红、白细胞在 10 个以下,经肠镜检查肠道黏膜有轻度炎症未有效;患者治疗后临床症状体征无好转,便常规以及肠镜检查患者肠道黏膜为未有明显好转甚至恶化为无效。

**1.4.5 安全性评价** 治疗后对患者的血、尿常规等实验室指标进行检查,对患者出现的消化系统不适,头晕、头疼、发热等不良反应的发生率进行检测。

### 1.5 统计学分析

计量数据以均数 $\pm$ 标准差( $\bar{x} \pm s$ )表示,采用 t 检验;计数资料采用%表示,采用卡方检验。采用 SPSS 19.0 统计软件所,所有数据比较,以  $P<0.05$  认为差异有统计学意义。

## 2 结果

### 2.1 两组患者治疗前后 CRP 水平比较

治疗后,两组患者的 CRP 水平与治疗前相比均下降( $P<0.05$ );与对照组相比,实验组患者的 CRP 水平较低( $P<0.05$ ),见表 1。

表 1 患者治疗前后血清 CRP 水平比较( $\mu\text{g/L}$ ,  $\bar{x} \pm s$ )

Table 1 Comparison of the serum levels of CRP between two groups before and after treatment( $\mu\text{g/L}$ ,  $\bar{x} \pm s$ )

| Groups             | Before treatment | After treatment       |
|--------------------|------------------|-----------------------|
| Experimental group | $69.54 \pm 8.86$ | $35.33 \pm 8.12^{*#}$ |
| Control group      | $67.12 \pm 9.32$ | $46.63 \pm 7.65^{*}$  |

Note: compared with before treatment,  $^{*}P<0.05$ ; compared with the control group after treatment,  $^{*#}P<0.05$ .

### 2.2 两组患者治疗前后 TNF- $\alpha$ 、IL-10 水平比较

治疗后,与治疗前相比,两组患者的 TNF- $\alpha$  水平均下降,

IL-10 水平均升高 ( $P<0.05$ ),与对照组相比,实验组患者的 TNF- $\alpha$  水平较低,IL-10 水平较高( $P<0.05$ ),见表 2。

表 2 患者治疗前后血清 TNF- $\alpha$ 、IL-10 水平比较( $\text{pg/mL}$ ,  $\bar{x} \pm s$ )

Table 2 Comparison of the serum levels of TNF- $\alpha$  and IL-10 between two groups before and after treatment( $\text{pg/mL}$ ,  $\bar{x} \pm s$ )

| Groups             | Time             | TNF- $\alpha$         | IL-10                 |
|--------------------|------------------|-----------------------|-----------------------|
| Experimental group | Before treatment | $34.53 \pm 5.53$      | $33.81 \pm 8.04$      |
|                    | After treatment  | $18.64 \pm 5.55^{*#}$ | $73.62 \pm 9.42^{*#}$ |
| Control group      | Before treatment | $35.36 \pm 4.38$      | $32.26 \pm 9.01$      |
|                    | After treatment  | $25.14 \pm 5.12^{*}$  | $64.06 \pm 8.82^{*}$  |

Note: compared with before treatment,  $^{*}P<0.05$ ; compared with the control group after treatment,  $^{*#}P<0.05$ .

### 2.3 两组患者临床疗效比较

实验组的治疗总有效率与对照组相比较高 ( $P<0.05$ ), 见

表3。

表 3 患者临床疗效比较(% ,  $\bar{x}\pm s$ )

Table 3 Comparison of the clinical curative effect between two groups(% ,  $\bar{x}\pm s$ )

| Groups             | Excellence | Effective | Invalid  | Total effective rate |
|--------------------|------------|-----------|----------|----------------------|
| Experimental group | 36(60.0)   | 20(33.33) | 4(6.67)  | 56(93.33)*           |
| Control group      | 25(41.67)  | 20(33.33) | 15(25.0) | 45(75.0)             |

Note: compared with the control group, \* $P<0.05$ .

### 2.4 两组患者临床安全性评价

两组患者在治疗期间,血、尿常规等实验室指标均未发生异常。对照组患者出现胃肠道不适 5 例,恶心 6 例,呕吐 3 例,头痛头晕 5 例;实验组患者出现胃肠道不适 2 例,恶心 2 例,两组患者的不良反应发生率分别为 31.67%(19/60) 以及 6.67%(4/60),实验组不良反应发生率较低( $P<0.05$ )两组患的不良反应经临床对症处理后,均好转,为对实验造成影响。

## 3 讨论

肠道菌群异常、抗原刺激,加之多种致病因素的共同作用而导致肠道免疫反应异常,大量炎症细胞趋化,肠上皮以及肠道组织细胞发生损伤,导致溃疡性结肠炎的发生,是临床上较为难愈的消化系统疾病,且后期患者并发症较多,甚至发生肠道粘膜纤维化以及癌变,因此其治疗已经成为目前医学研究的热点问题<sup>[6]</sup>。溃疡性结肠炎的发病机制较为复杂,其中免疫、环境、遗传、肠道菌群失调等因素已经证实与本病的发病关系密切<sup>[7]</sup>。目前临床对于溃疡性结肠炎的治疗多采用 5-氨基水杨酸类的抗炎药物或糖皮质激素、免疫抑制剂等<sup>[8]</sup>。柳氮磺吡啶为 5-氨基水杨酸类的抗炎药物,其活性成分为 5-氨基水杨酸(5-ASA),其通过载体分子到达患处,作用于发生炎症的肠粘膜,抑制白细胞的激活和炎性因子的释放,起到抗炎作用。但其载体磺胺吡啶会引起一系列的不良反应,使患者不能耐受<sup>[9]</sup>。美沙拉嗪通过偶氮连接两分子的 5-氨基水杨酸,使有效成分在结肠内才能分解,不会在胃中或小肠中被提前吸收,对受损的肠道粘膜定向持续的释放 5-氨基水杨酸,抑制肠道内的多种炎症介质的表达,进而达到缓解患者病情,治疗溃疡性结肠炎的目的,临床试验已经证实其有效,不仅提高了疗效,并且减少了副作用<sup>[10-11]</sup>。我们的实验结果表明,实验组患者临床治疗有效率较高,且不良反应发生率较低,这与文献报道的结果一致。

多数学者认为,细胞因子水平的失衡在溃疡性结肠的发病过程中具有重要作用,炎性因子失衡,促炎因子的水平升高会损害患者的肠道黏膜,导致该病的发生<sup>[12]</sup>。并且其炎症反应程度的高低与患者的病情严重程度以及预后等都具有相关性<sup>[13]</sup>。研究已经证实,肿瘤坏死因子- $\alpha$  (TNF- $\alpha$ ) 和 C-反应蛋白(CRP)水平的高低可以判断溃疡性结肠炎患者的病情,对患者的病情以及疗效进行评价<sup>[14]</sup>。目前,研究已经发现的 TNF- $\alpha$  的主要作用机制包括趋化炎性细胞,调节细胞因子水平,增加内皮细胞黏附作用,促进肠道上皮细胞的凋亡等<sup>[15]</sup>。我们的实验结果表明,治疗后两组患者的 TNF- $\alpha$  水平均下降,其中实验组

患者的 TNF- $\alpha$  水平较低。TNF- $\alpha$  能够与肠道细胞表面的 TNF-R1 结合,改变患者肠道上皮细胞的通透性,产生对肠道粘膜的损害作用;同时,TNF- $\alpha$  还能够刺激中性粒细胞,使其产生趋化作用,活化 T 细胞,促进炎症介质的生成,启动细胞免疫,使肠粘膜发生免疫紊乱,进一步促进肠道上皮的炎症反应,破坏肠粘膜屏障功能,对肠道粘膜产生侵袭作用,加剧患者的病情<sup>[16-18]</sup>。此外,TNF- $\alpha$  还能够促进炎性因子,如 IL-10 的水平升高,诱导肠上皮的持续损伤。美沙拉嗪的抗炎作用能够抑制以上的炎症过程,因此能够降低患者的 TNF- $\alpha$  的水平。C 反应蛋白(CRP)是一种由多种细胞介导的急性时相蛋白,由肝细胞合成,参与了多种炎症反应,是机体比较灵敏的感染性、炎症性疾病的炎性非特异性指标,已有研究证实<sup>[19]</sup>,CRP 水平的高低与溃疡性结肠炎的缓解期和活动期相关。另外,还有学者的研究表明,CRP 的水平越高,患者发生溃疡性结肠炎癌变的几率就越大。我们的研究证实,治疗后,两组患者的 CRP 水平均下降。已有研究证实,在正常人血中 CRP 的含量较低,当机体受到炎症和感染时,其水平明显升高。CRP 能够与 T 细胞结合,发挥细胞功能,同时 CRP 能够诱导多种细胞因子进而发生促炎作用。当炎症反应被抑制是,患者的 CRP 水平下降,表明本实验的治疗措施能够降低降低患者肠道内的炎症反应。

白细胞介素-10(IL-10)是公认的炎症抑制因子,其能够抑制活化的单核细胞以及粒细胞的产生 GM-CSF、G-CSF,抑制单核产生趋化因子,进而抑制其向炎症的发生部位聚集<sup>[20]</sup>。同时,IL-10 还能够抑制单核细胞等细胞分泌合成 TNF- $\alpha$  等促炎因子,抑制炎症反应。我们的实验结果表明,治疗后,两组患者的 IL-10 水平均升高,其中实验组患者的 IL-10 水平较高,证实美沙拉嗪的抗炎作用较好。

综上,本实验通过探讨溃疡性结肠炎患者血清 CRP、IL-10 及 TNF- $\alpha$  水平的变化,证实了美沙拉嗪能够抑制溃疡性结肠炎患者的炎症反应水平,降低 CRP、TNF- $\alpha$  水平,升高 IL-10 水平,临床疗效较好,且用药安全。未来我们将对本实验的结论作更深入的论证。

### 参考文献(References)

- [1] Bressler B, Marshall J K, Bernstein C N, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus [J]. Gastroenterology, 2015, 148(5): 1035-1058. e3
- [2] Sandborn W J, Feagan B G, Wolf D C, et al. Ozanimod Induction and Maintenance Treatment for Ulcerative Colitis [J]. New England Journal of Medicine, 2016, 374(18): 1754-1762

- [3] Goyette P, Boucher G, Mallon D, et al. High-density mapping of the MHC identifies a shared role for HLA-DRB1 [ast] 01: 03 in inflammatory bowel diseases and heterozygous advantage in ulcerative colitis[J]. *Nature genetics*, 2015, 47(2): 172-179
- [4] Cioffi M, Rosa A D, Seroo R, et al. Laboratory markers in ulcerative colitis: Current insights and future advances [J]. *World journal of gastrointestinal pathophysiology*, 2015, 6(1): 13-22
- [5] Kevans D, Waterman M, Milgrom R, et al. Serological markers associated with disease behavior and response to anti tumor necrosis factor therapy in ulcerative colitis[J]. *Journal of gastroenterology and hepatology*, 2015, 30(1): 64-70
- [6] Gibson D J, Heetun Z S, Redmond C E, et al. An accelerated infliximab induction regimen reduces the need for early colectomy in patients with acute severe ulcerative colitis [J]. *Clinical Gastroenterology and Hepatology*, 2015, 13(2): 330-335. e1
- [7] Tariq R, Smyrk T, Pardi D S, et al. New-Onset Microscopic Colitis in an Ulcerative Colitis Patient After Fecal Microbiota Transplantation [J]. *The American journal of gastroenterology*, 2016, 111(5): 751-752
- [8] Arias M T, Castele N V, Vermeire S, et al. A panel to predict long-term outcome of infliximab therapy for patients with ulcerative colitis [J]. *Clinical Gastroenterology and Hepatology*, 2015, 13(3): 531-538
- [9] Lord J, Chen J, Thirlby R C, et al. T-cell receptor sequencing reveals the clonal diversity and overlap of colonic effector and FOXP3+ T cells in ulcerative colitis [J]. *Inflammatory bowel diseases*, 2015, 21(1): 19-30
- [10] Taylor K M, Sparrow M P. Editorial: tacrolimus vs. anti tumour necrosis factor agents for moderately to severely active ulcerative colitis [J]. *Alimentary pharmacology & therapeutics*, 2016, 43(9): 1016-1017
- [11] Travis S P L, Schnell D, Feagan B G, et al. The impact of clinical information on the assessment of endoscopic activity: characteristics of the ulcerative colitis endoscopic index of severity [UCEIS] [J]. *Journal of Crohn's and Colitis*, 2015, 9(8): 607-616
- [12] Skowron K B, Lapin B, Rubin M, et al. Clostridium Difficile Infection in Ulcerative Colitis: Can Alteration of the Gut-associated Microbiome Contribute to Pouch Failure? [J]. *Inflammatory bowel diseases*, 2016, 22(4): 902-911
- [13] Cesarini M, Collins G, Ronnblom A, et al. Predicting the risk of acute severe colitis (ASC) at diagnosis of Ulcerative Colitis (UC): external validation[J]. *Journal of Crohn's and Colitis*, 2015, 9(1): S77-S443
- [14] Kisiel J B, Loftus E V. Editorial: Clarity and Caution in the Natural History of Low-Grade Dysplasia in Ulcerative Colitis [J]. *The American journal of gastroenterology*, 2015, 110(10): 1473-1474
- [15] Lasso A, Stotzer P O, Öhman L, et al. The intra-individual variability of faecal calprotectin: a prospective study in patients with active ulcerative colitis[J]. *Journal of Crohn's and Colitis*, 2015, 9(1): 26-32
- [16] Brandse J F, van den Brink G R, Wildenberg M E, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis[J]. *Gastroenterology*, 2015, 149(2): 350-355. e2
- [17] Leowardi C, Schneider M L, Hinz U, et al. Prognosis of Ulcerative Colitis-Associated Colorectal Carcinoma Compared to Sporadic Colorectal Carcinoma: A Matched Pair Analysis [J]. *Annals of surgical oncology*, 2016, 23(3): 870-876
- [18] 张凌玲, 王素娟, 龙再菊, 等. 溃疡性结肠炎患者外周血 C 反应性蛋白、血清降钙素原及白细胞介素 -6 水平及临床意义[J]. *现代生物医学进展*, 2016, 16(26): 5166-5168
- Zhang Ling-ling, Wang Su-juan, Long Zai-ju, et al. Levels and Significance of Serum PCT, CRP and IL-6 in Patients with Ulcerative Colitis[J]. *Progress in Modern Biomedicine*, 2016, 16(26): 5166-5168
- [19] Cleynen I, Boucher G, Jostins L, et al. Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: a genetic association study[J]. *The Lancet*, 2016, 387(10014): 156-167
- [20] Kobayashi T, Suzuki Y, Motoya S, et al. First trough level of infliximab at week 2 predicts future outcomes of induction therapy in ulcerative colitis-results from a multicenter prospective randomized controlled trial and its post hoc analysis [J]. *Journal of gastroenterology*, 2016, 51(3): 241-251

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- [36] Assawachananont J, Mandai M, Okamoto S, et al. Transplantation of embryonic and induced pluripotent stem cell-derived 3D retinal sheets into retinal degenerative mice [J]. *Stem Cell Reports*, 2014, 2(5): 662-674
- [37] Zhong X, Gutierrez C, Xue T, et al. Generation of three-dimensional retinal tissue with functional photoreceptors from human iPSCs[J]. *Nat Commun*, 2014, 5: 4047
- [38] Zhou L, Wang W, Liu Y, et al. Differentiation of induced pluripotent stem cells of swine into rod photoreceptors and their integration into the retina[J]. *Stem Cells*, 2011, 29(6): 972-980
- [39] Hara A, Aoli H, Takamatsu M, et al. Human embryonic stem cells transplanted into mouse retina induce neural differentiation [J]. *Stem Cells Cancer Stem Cells*, 2012, 2: 291-298
- [40] Croze RH, Buchholz DE, Radeke MJ, et al. ROCK inhibition extends passage of pluripotent stem cell-derived retinal pigmented epithelium [J]. *Stem Cells Transl Med*, 2014, 3(9): 1066-1078
- [41] Zhong X, Gutierrez C, Xue T, et al. Generation of three-dimensional retinal tissue with functional photoreceptors from human iPSCs[J]. *Nat Commun*, 2014, 5: 4047
- [42] Song MJ, Bharti K. Looking into the future: Using induced pluripotent stem cells to build two and three dimensional ocular tissue for cell therapy and disease modeling [J]. *Brain Res*, 2016, 1638(Pt A): 2-14
- [43] Reichman S, Goureau O. Production of Retinal Cells from Confluent Human iPS Cells[J]. *Methods Mol Biol*, 2016, 1357: 339-351