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夏枯草胶囊对自身免疫性甲状腺炎大鼠甲状腺组织及 Fas、FasL 表达的影响 *

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摘要 目的：探讨夏枯草胶囊对自身免疫性甲状腺炎(AITD)大鼠甲状腺组织病理学及 Fas、FasL 表达的影响。**方法：**将 40 只雌性 SD 大鼠按照随机数表法随机分为空白对照组、模型组、夏枯草胶囊组、硒酵母组，每组 10 只，空白对照组予以正常饲养，模型组和药物组予以 PTg 皮下注射建立 AITD 模型，夏枯草胶囊组、硒酵母组分别给予夏枯草胶囊与硒酵母片的生理水溶液灌胃，药物干预 6 周后处死大鼠，取甲状腺组织，HE 染色电镜下观察各组大鼠甲状腺组织形态，免疫组化法检测各组大鼠甲状腺组织 Fas、FasL 蛋白的表达。**结果：**1)模型组大鼠甲状腺组织滤泡大量破坏，形态不规则，胶质分布不均匀，滤泡间隙增大，可见大量淋巴细胞及浆细胞浸润。夏枯草胶囊组滤泡形态尚规则，胶质含量较空白组少，滤泡间有少量淋巴细胞浸润。与模型组对比，夏枯草胶囊组与硒酵母组滤泡破坏及淋巴细胞浸润有显著改善。2)对照组大鼠甲状腺组织中 Fas、FasL 蛋白仅呈少量表达，模型组大鼠甲状腺组织中 Fas、FasL 蛋白表达较对照组显著增加(P<0.01)，夏枯草胶囊组大鼠甲状腺组织中 Fas、FasL 蛋白表达较模型组及硒酵母组均显著减少(P<0.01)。**结论：**夏枯草胶囊可能通过减少 Fas、FasL 的表达，抑制甲状腺滤泡细胞凋亡，从而减轻甲状腺滤泡上皮的破坏。

关键词：自身免疫性甲状腺炎；Fas；FasL；夏枯草胶囊

中图分类号：R-33；R581.4 **文献标识码：**A **文章编号：**1673-6273(2018)07-1239-04

Effect of Prunella Vulgaris Capsule on Thyroid Tissue and Expression of Fas /FasL in Rats with Autoimmune Thyroiditis*

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ABSTRACT Objective: To study and observe the effect of prunella vulgaris capsule on the thyroid tissue and expression of Fas /FasL in rats with autoimmune thyroiditis. **Methods:** Forty female SD rats were divided into the control group, AITD model group, Prunella vulgaris capsule group and selenium yeast group. The AITD model was made by subcutaneous injection of PTg. Prunella vulgaris capsule group and selenium yeast group were treated with Prunella vulgaris and selenium yeast. The rats were sacrificed at 6 weeks after the drug intervention. The thyroid tissue was observed by HE staining. The expression of Fas and FasL protein in the thyroid tissue of the rats were observed by immunohistochemistry. **Results:** 1) The thyroid tissue follicles were greatly destroyed in the model group with irregular shape, uneven distribution of glial, increased follicular gap, and a large number of lymphocytes and plasma cell infiltration. The follicular morphology in Prunella vulgaris capsule group was still regular, and the glial content was lower than that of the control group, there was a small number of lymphocyte infiltration between the follicles. Prunella vulgaris capsule and selenium yeast group showed significant improvement in the follicular destruction and lymphocyte infiltration. 2) In the control group, Fas and FasL protein in thyroid tissue only expressed a small amount; the expressions of Fas and FasL protein in thyroid tissue of model group was significantly higher than that of the control group (P<0.01); the expressions of Fas and FasL protein in thyroid tissue of Prunella vulgaris capsule group were significantly lower than those of the model group and selenium yeast group (P<0.01). **Conclusion:** Prunella vulgaris capsules may reduce the damage of thyroid follicular epithelium by reducing the expression of Fas and FasL and inhibiting the apoptosis of thyroid follicle cells.

Key words: Autoimmune thyroiditis; Fas; FasL; Prunella vulgaris capsules

Chinese Library Classification(CLC): R-33; R581.4 Document code: A

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前言

自身免疫性甲状腺炎(AITD)以慢性淋巴细胞性甲状腺炎(HT)为主,国外统计其发病率可达 5%[1],病因尚不明确,病机复杂,其主要特征为特异性甲状腺自身抗体升高以及甲状腺组织中的大量淋巴细胞浸润[2],早期可有甲亢症状,随着甲状腺滤泡破坏,逐渐发展为甲减。大量研究证实随着病情的发展,桥本氏甲状腺与甲状腺癌发生密切相关[3,4]。

Fas/FasL 是肿瘤坏死因子家族中的一对跨膜蛋白[5],细胞通过其表达的 FasL 与另一细胞上的 Fas 结合发挥毒性 T 淋巴细胞使其凋亡[6],被认为是 AITD 的发病机制之一,目前尚无针对该机制有明确疗效的西药,现代医学在理论上提出免疫调节剂针对其免疫因素进行治疗,然而因药物毒副作用受到一定争议。我们前期的研究发现夏枯草胶囊有降低 HT 患者自身抗体滴度的作用,可调整 Th 相关细胞因子表达。本研究将以 AITD 模型大鼠为观察对象,探讨夏枯草胶囊对自身免疫性甲状腺炎(AITD)大鼠甲状腺组织病理学及 Fas、FasL 表达的影响。

1 资料与方法

1.1 实验动物

SPF 级 SD 雌性大鼠 40 只,4-6 周,体重 100-120 g,由湖北省疾病控制中心提供,来源证号:NO.42000600015772,饲养于湖北中医药大学实验动物中心 SPF 级动物房。

1.2 实验主要药品、试剂及仪器

硒酵母片 (西维尔):由牡丹江灵泰药业有限公司提供,批号:国药准字 H10940161,规格:50 μg;夏枯草胶囊:由北京紫辰宣医药经营有限公司提供,批号:国药准字 Z19991033,规格:每粒装 0.35 g;碘化钠、猪甲状腺球蛋白(PTg)、PBS 缓冲液,完全弗氏佐剂(CFA)、不完全弗氏佐剂(IFA),由 sigma 公司提供;DAB 浓缩型试剂盒,bioswamp 公司提供,PAB180021;兔 Fas 多克隆抗体,abcam 公司提供,ab82419;兔 Fasl 多克隆抗体,abcam 公司提供,ab15258;石蜡切片机,徕卡显微系统有限公司,型号 RM2235;摊片机,湖北康强医疗器械有限公司,型号 TKD-TK;正置显微镜,OLYMPUS 公司,型号 CX41。

1.3 造模及给药方法

1.3.1 造模方法 初次免疫时取 PTg 与 CAF 等体积混合充分乳化,于大鼠足垫部、背部皮下多点注射 PTg100 μg/ 只,每周 1 次,连续 2 周,加强免疫时取 PTg 与 IAF 等体积混合充分乳化,于大鼠皮下多点注射 PTg100 μg/ 只,从第 3 周开始至第 6 周结束,并给予 0.64 g/L 的碘化钠高碘水喂养。

1.3.2 给药方法 空白组及模型对照组按照 1 mL/100 g 体重灌服生理盐水,药物组给药剂量按照人服用最大剂量的人和大鼠体表面积换算,夏枯草胶囊使用时去外胶囊,将药粉末配制成 50 mg/mL 的夏枯草溶液,1 mL/100 g·d 剂量给夏枯草组各大鼠灌胃,将硒酵母片配制成 20 μg/mL 的硒酵母溶液,1 mL/l00 g·d 剂量给硒酵母组各大鼠灌服,各组连续药物干预 6 周。

1.4 取材及检测方法

1.4.1 HE 染色 实验结束后大鼠禁食水 24 h,处死,锋利的刀、剪切取大鼠甲状腺组织,于 10%中性福尔马林中固定 1-2 天,按常规步骤脱水浸蜡包埋,前将包埋好的组织样本置于-20℃冷冻数分钟,切成 4~5 μm 厚度的组织片。将组织切片常规脱蜡至水,稍水洗 1-2 min ,苏木精液染色 3-6 min ,流水洗去苏木精液 1-2 min ,1%盐酸酒精浸泡 1-3 S ,稍水洗 1-2 S,促蓝液返蓝 5-10 S , 流水冲洗 15-30 S ,0.5%伊红液染色 2-3 min ,蒸馏水稍洗 1-2 S ,不同浓度乙醇浸泡冲洗,二甲苯(Ⅰ)浸泡 2-3 S ,二甲苯(Ⅱ)浸泡 2-3 S ,最后中性树胶封固。光镜下观察并拍照。

1.4.2 免疫组化 将固定后的组织用流水冲洗,不同浓度的乙醇逐级脱水,50%、70%、85%、95%直至纯酒精(无水乙醇),透明处理后浸蜡,将浸透蜡的组织块包裹在石蜡中,-20 度冰箱中放置 30 min,切成 4-7 μm 厚的组织片,将玻片置于 65℃恒温烘箱中烤片 1 min;置于二甲苯 I 中浸泡 15 min,再置于二甲苯 II 中浸泡 15 min, 再用不同浓度的酒精浸泡脱蜡,0.01M 柠檬酸钠缓冲溶液中高压修复 15 min, 自然冷却后,0.02M PBS 洗 3 min× 3 次,将玻片置于 3% H_2O_2 中,湿盒孵育 10 min,以消除内源性过氧化物酶的活性。0.02 M PBS 冲洗 3 min^3 次。滴加 Fas/FasL 一抗, 湿盒孵育, 室温下放置 1 h,0.02 M PBS 冲洗 3min× 3 次, 滴加 maxvision 二抗, 湿盒孵育, 室温下放置 20 min-30 min。0.02M PBS 冲洗 3 min× 3 次,DAB 染色,苏木素复染 3 min,烘干后封片,光镜下观察拍照。

1.5 实验结果判定

光镜下观察甲状腺组织病理学改变及 Fas、FasL 免疫阳性物,根据阳性物的分布范围及着色强度进行计分,分数累加,无阳性细胞为 0 分, 阳性细胞≤ 25%记 1 分,26%～50%为 2 分,51%～75%为 3 分,＞75% 为 4 分。无色为 0 分, 淡黄色为 1 分,棕黄色为 2 分,棕褐色为 3 分[7]。

1.6 统计学方法

采用 SPSS 软件对最终数据进行统计分析,组间比较采用 t 检验,以 P<0.05 为差异有显着性意义,P<0.01 为差异有非常显着性意义。

2 结果

2.1 各组大鼠甲状腺组织病理学形态比较

如图 1 所示,正常组大鼠甲状腺组织可见排列规则紧密的甲状腺滤泡,滤泡中含有丰富胶质,分布均匀,滤泡间无淋巴细胞及浆细胞浸润,无纤维化病灶。模型组大鼠甲状腺组织滤泡大量破坏,形态不规则,胶质分布不均匀,滤泡间隙增大,可见大量淋巴细胞及浆细胞浸润。夏枯草胶囊组滤泡形态尚规则,胶质含量较空白组少,滤泡间有少量淋巴细胞浸润,与模型组对比滤泡破坏及淋巴细胞浸润有显著改善。硒酵母组滤泡形态欠规则,部分滤泡结构破坏,胶质含量减少,滤泡间可见淋巴细胞浸润,与模型组对比滤泡破坏及淋巴细胞浸润有一定改善。

2.2 各组大鼠甲状腺组织 Fas、FasL 蛋白的表达

如图 2、表 1 所示,对照组大鼠甲状腺组织中 Fas、FasL 蛋白仅呈少量表达, 模型组大鼠甲状腺组织中 Fas、FasL 蛋白表达较对照组显著增加(P<0.01),夏枯草胶囊组大鼠甲状腺组织中 Fas、FasL 蛋白表达较模型组及硒酵母组均显著减少(P<0.01)。

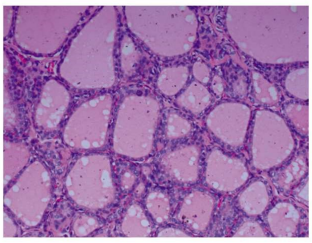

图 1-1 正常组× 200 倍
可见排列规则紧密的甲状腺滤泡，滤泡中含有丰富胶质，分布均匀，滤泡间无淋巴细胞及浆细胞浸润，无纤维化病灶。
(Fig. 1 -1 Blank control group× 200
Visible arrangement of tight rules of thyroid follicles, follicles are rich in gum, evenly distributed, no lymphocytes and plasma cells between the follicular infiltration, no fibrosis lesions.)

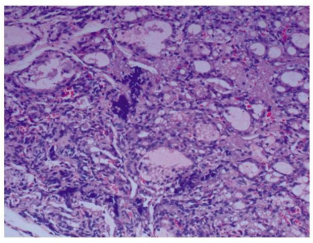

图 1-2 模型组× 200 倍
甲状腺滤泡大量破坏，形态不规则，胶质分布不均匀，滤泡间隙增大，可见大量淋巴细胞及浆细胞浸润。
(Fig. 1 -2 Model group× 200
Thyroid follicle was damaged, irregular shape, uneven distribution of glial, follicular gap increased, showing a large number of lymphocytes and plasma cell infiltration.)

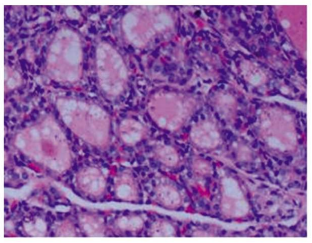

图 1-3 夏枯草胶囊组× 200 倍
滤泡形态尚规则，胶质含量较空白组少，滤泡间有少量淋巴细胞浸润，与模型组对比滤泡破坏及淋巴细胞浸润有显著改善。(Fig. 1 -3
Prunella vulgaris group× 200
Follicular morphology is still rules, colloidal content were less than the blank group, there is a small amount of lymphocytes between the follicles infiltration, compared with the model group, follicular damage and lymphocyte infiltration was significantly improved.)

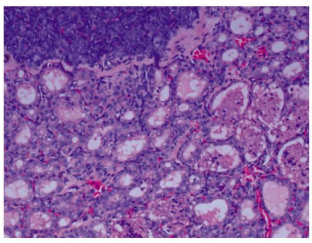

图 1-4 硒酵母组× 200 倍
滤泡形态欠规则，部分滤泡结构破坏，胶质含量减少，滤泡间可见淋巴细胞浸润，与模型组对比滤泡破坏及淋巴细胞浸润有一定改善。
(Fig. 1 -4 Selenium yeast group× 200
Follicular morphology is less regular, part of the follicle structure were damaged, colloidal content decreased, between the follicles visible lymphocyte infiltration, compared with the model group follicle damage and lymphocyte infiltration have been improved.)

图 1 光镜下各组大鼠甲状腺组织病理学改变

Fig. 1 Pathological changes of thyroid tissue in rats under light microscope

表 1 各组大鼠甲状腺组织 Fas、FasL 蛋白的表达积分

Table 1 Expression of Fas and FasL proteins in thyroid tissue in each group

The group	Fas	FasL
Blank control group	0.3± 0.48	0.4± 0.52
Model group	4.8± 1.03**	5.0± 0.82**
Prunella vulgaris group	2.5± 0.84**##	2.7± 1.06**##
Selenium yeast group	3.5± 0.84**##&	3.6± 0.84**##&

Note: *P<0.01, **P<0.05 vs blank control group; #P<0.05, ##P<0.01 vs model group; &P<0.05, &&P<0.01 vs prunella vulgaris group.

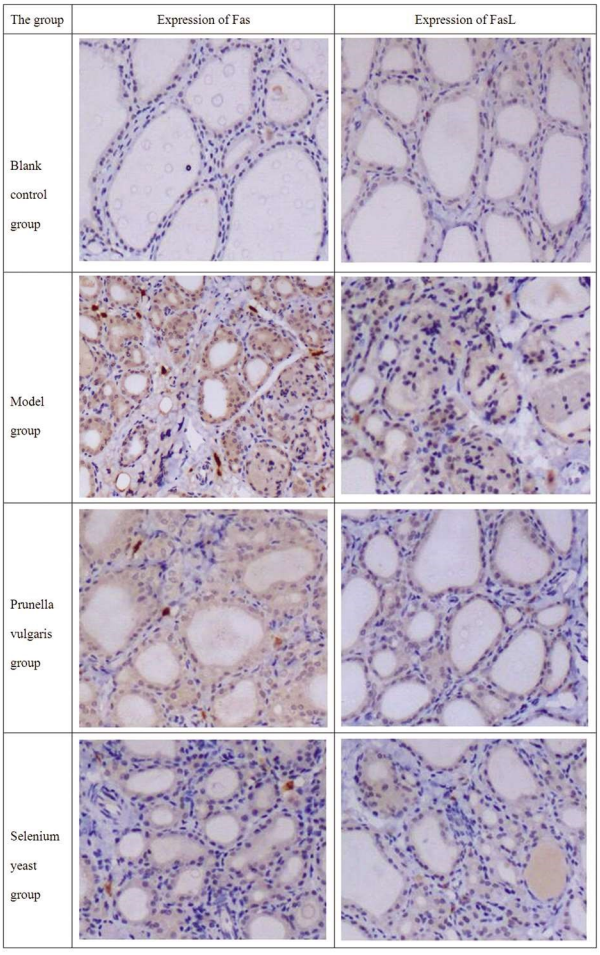

图 2 各组大鼠甲状腺组织 Fas、FasL 蛋白的表达(× 200 倍)

Fig. 2 Expressions of Fas and FasL proteins in the thyroid tissue of rats in each group(× 200)

3 讨论

光镜下淋巴细胞的浸润及电镜下淋巴细胞对甲状腺滤泡上皮的攻击现象是 AITD 免疫反应异常的重要形态学指标[8]，广泛的甲状腺上皮细胞损伤，细胞凋亡，造成甲状腺组织损伤，是桥本甲状腺炎发病的重要机制，当滤泡开时破坏时，T3、T4 过多的释放入血液，造成一过性的甲亢，随着滤泡的逐渐破坏，甲状腺形态与功能发生改变，合成 T3、T4 的能力减弱，逐渐发展为甲减。因此，从 AITD 的病理形态学来探讨其疗效具有重要意义。目前诸多国内研究证实中药可以改善甲状腺组织的破坏[9]。夏枯草苦、辛，寒。入肝、胆经，具有清肝明目，散结消肿的功效，是治疗甲状腺相关疾病的要药，夏枯草胶囊是夏枯草提取物，主要成份是夏枯草总皂甙，临床运用于 HT 的治疗可降低自身抗体滴度，调节患者免疫功能。

在本实验中，硒酵母组与模型组对比滤泡破坏及淋巴细胞浸润有一定改善；夏枯草胶囊组滤泡形态尚规则，与模型组对比滤泡破坏及淋巴细胞浸润有显著改善，证明夏枯草胶囊可明

显改善受损的滤泡，并减轻淋巴浸润，且效果优于硒酵母片，可见经药物干预后，甲状腺组织破坏可以得到不同程度的恢复，证明这种破坏改变是一个可逆的过程，而一些研究认为一旦甲状腺组织发生纤维化改变就难以逆转[10]，提示对于 AITD 患者早期干预治疗具有重要意义。滤泡上皮细胞的破坏与细胞凋亡密切相关，凋亡信号过度表达，会引起自身免疫性疾病。Fas/FasL 是一种重要的外源性细胞凋亡途径[11,12]，Fas 属于肿瘤坏死因子成员之一，在胞浆区有死亡域，通过与其受体 FasL 结合来激活[13,14]，细胞通过其表达的 FasL 与另一细胞上的 Fas 结合使另一细胞死亡[15,16]。Fas 与其配体同时可以激活 Fas 相关蛋白、FADD、Caspase-8、Caspase-3 等，致细胞发生细胞凋亡[17]，也可以控制效应 T 细胞群体，在免疫反应期间产生各种炎性细胞因子和生长因子，导致多种炎症的产生[18,19]。研究显示 IFN-γ(干扰素 -γ)可以上调 Fas 的表达[20,21]，而干扰素 -γ 属于 Th 相关细胞因子。在我们的前期研究中，发现 AITD 模型组大鼠包括 IFN-γ 在内的 Th 相关细胞因子表达水平是显著高于正常组的。显示同样是甲状腺疾病，桥本氏甲状腺炎患者中 FasL 表达的 mRNA 的表达是 Graves 病患者的 2 倍，也再次证实了 HT 患者甲状腺组织的破坏是与 Fas/FasL 的高表达密切相关[22]，曹慧云[23]等研究发现血清 Fas 浓度与 HT 甲状腺纤维化程度呈正相关。

关于针对 Fas/Fas 机制的治疗，国内诸多研究者，贾燕丽、王家红等[24,25]也证实了中医卓越的功效。虽然目前有相关中药研究，但对于单味中药的相关动物实验研究还比较匮乏，通过对成分简单的单味中药进行研究可以更容易阐述中药的作用机理，为以后更长远的中药研究打下基础，而成分稳定，临床疗效肯定的夏枯草胶囊则是一个较好的研究开端，在本实验中，正常大鼠的甲状腺中不表达或极少量表达 Fas、FasL 蛋白，而 AITD 模型大鼠甲状腺组织中 Fas、FasL 蛋白表达明显增加，经夏枯草干预后，大鼠甲状腺中 Fas、FasL 蛋白表达显著减少，效果优于硒酵母。综上所述，夏枯草胶囊可能通过减少 Fas、FasL 的表达，抑制甲状腺滤泡细胞凋亡，从而减轻甲状腺滤泡上皮的破坏。由于 Fas 信号通路在肿瘤中的作用，我们推测运用夏枯草胶囊是否可以预防 AITD 癌变，在未来的研究中，我们将进一步研究 AITD 通过 Fas 信号发生癌变的机制及夏枯草的干预作用。

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是否可以辅助提高老年人的内源性注意。

综上所述,在照顾或者提高老年人注意力时,对注意的不同类型进行评估和分类以采取合适的治疗策略是很重要的,并且将这种注意任务用于检测有注意功能障碍的患者可能能够更精确地判断患者注意障碍的机制,从而在康复工作中对患者的康复指导更有针对性,用最有效的手段解决患者的注意问题。

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