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调节慢性炎症防治衰老相关疾病的研究进展

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摘要: 衰老是应激、损伤、感染、免疫反应衰退以及代谢障碍等综合作用积累的结果。细胞在衰老的过程中会分泌大量的炎性因子。相关研究表明,老年人的皮肤及粘膜对细菌、病毒感染、外伤等等方面的抵抗和防御能力明显低于青年人,炎性因子不断增多, 加速细胞衰老。由此可见, 控制慢性炎症可能是干预衰老的有效途径。生物活性透明质酸可能通过诱导防卫素分泌和与CD44/TLR4 受体结合,抑制细菌生长和炎症进展,从而发挥抗衰老作用。本文对有关慢性炎症和衰老之间的关系的研究进行综述,探讨生物活性透明质酸对慢性炎症的调节作用及其抗衰老机制。

关键词: 炎症;衰老;生物活性透明质酸

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Anti-aging by Regulating Age-related Chronic Inflammation

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ABSTRACT: Senescence is the result of the accumulation of metabolic disorders such as the stress, injury, infection, immune response to recession and other comprehensive effects. Cells in the process of aging could secrete large numbers of inflammatory factors. The related studies have shown that the resistance and defensive ability of elderly people's skin and mucous membrane of bacteria are significantly lower than that of the youngs. The more inflammotary, the quicker aging. Therefore, it is indicated that the control of chronic inflammation may be an effective method of anti-aging. Bioactive hyaluronic acid may inhibit inflammation and growth of bacteria by binding to CD44/ TLR4 receptor and inducing secretion of beta-defensin. This paper reviewed the recent publications about the relationships between the chronic inflammation and the aging so as to explore the bioactive hyaluronic acid the adjustment role of chronic inflammation and the mechanisms of anti-aging.

Key words: Inflammation; Aging; Bioactive hyaluronic acid

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人类生存在一个充满微生物的世界中,每个生命的延续都是特异性和非特异性免疫力与外来微生物引起的组织损伤相互作用的过程。在这个过程中,炎症扮演了重要角色。炎症是由病毒、细菌以及其它微生物入侵组织或者组织损伤而引发的一种非特异性免疫反应,常见的皮肤伤口表现为局部红、肿、痛,伴有白聚集和致炎因子增多就是典型的炎症反应。

人类在进化的过程中, 无老年疾病干扰的寿命范围是在40-50 岁之间[1]。随着寿命的延长,牙周病、皮肤炎症、阴道炎、干眼病、咽炎、气管炎、胃炎、结肠炎、关节炎、动脉粥样硬化、糖尿病、肥胖、老年痴呆和癌症等炎性疾病的发病率也随之升高[2]。正常的炎症反应是用来保护人类不受致命伤害的一种非特异性免疫反应,而非正常的、过度的炎症反应则是引起众多老年疾病的主要因素[3]。这提示我们,有效地控制慢性炎症发展可能是干预衰老和衰老相关疾病的途径之一。

1 炎症与衰老性疾病

生命过程中炎症性疾病低发的老年人群寿命相对延长[4],其心脑血管疾病和癌症的发病率也相对低[5]。以腹部脂肪堆积、高血脂、高血糖、高血压等为特征的代谢综合征也在老年多发,其中慢性炎症扮演了重要角色[6]。人类衰老最重要的是心脑血管衰老,动脉粥样硬化是心血管衰老的根本原因[7]。动脉粥样硬化,是人类心脑血管衰老的最重要的病因,脂类沉积、高血压、吸烟产生的自由基损伤血管内皮,产生局部炎症反应,造成动脉粥样硬化[8]。炎症反应也参与了其它衰老相关疾病的病理过程,包括糖尿病、肾病、老年痴呆和癌症等[9]。衰老过程中由于机体先大性免疫系统及获得性免疫系统失衡引起促炎性细胞因子释放,老年人血浆炎性因子水平普遍有轻度增高,其原因和性激素水平降低、抽烟和慢性炎症相关联,包括动脉粥样硬化、无症状菌尿症和脂肪组织相对增加[10-13]。Dixit 等[14]研究发现,通过基因调控减少小鼠炎症基因 Nlrp3 表达,明显减少高龄小鼠衰老相关疾病发生,表明炎症是衰老相关的疾病因。药物控制

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良好的艾滋病人由于特异性免疫力缺失，其非特异性免疫，即炎症反应明显增强，表现为衰老相关疾病明显多发，包括心血管疾病、肿瘤、骨质疏松等，提示炎症反应增高是衰老相关疾病的病因之一。

现代医学已经发现了炎症反应的标志物，即血浆炎症反应蛋白（CRP）、血浆肿瘤坏死因子（TNF-α）和白介素 6（ IL-6）[15]。炎症细胞分泌的炎症因子可以引发血浆中炎症反应蛋白升高，炎症反应蛋白还能进一步激活人体固有的能产生炎症的非特异性免疫系统。炎症反应蛋白在急性和慢性炎症过程中均有不同程度升高，是人体有炎症疾病的标志物，也有可能成为人类衰老需要抗炎干预的标志物。除动脉粥样硬化外，其它皮肤粘膜炎症，如牙龈粘膜炎症、皮肤炎症、阴道炎症、眼结膜炎症、关节炎症、上呼吸道粘膜炎症和肠道炎症性疾病也是衰老的重要原因[16]，还有可能是引起和加重动脉粥样硬化造成的心脑血管疾病的病因，防治这些慢性炎症疾病是一种抗衰老相关疾病的途径。

2 炎症相关危险因素

2.1 空气污染

人类每小时平均吸入 0.52 升空气，中国空气中的污染物质和微生物是刺激呼吸道炎症发生和发展的主要原因之一。中国空气污染严重，雾霾天气反复侵袭大中城市，鼻炎咽炎普遍。 中国是烟草生产和消费大国，总吸烟人数为 3.56 亿，被动吸烟，引发上呼吸道粘膜和血管内皮炎症[17]。

2.2 水污染

水和空气一样是生命之源，人类每天平均摄入 2.2 升水，摄入水中的化学污染物、微生物和微生物产物是引起消化道炎症疾病（包括克山病和大骨节病等地方病）发生发展的原因之一[18]。

2.3 工作压力

现代中国人缺少适当户外运动，工作压力大，造成特征为腹部脂肪堆积、高血脂、高血糖、高血压为特征的代谢综合征多发，其中慢性炎症扮演了重要角色。有证据表明，运动可以控制这种代谢综合征的发病率，明显降低血浆炎症因子水平[19]。适当运动还可以缓解工作压力引起的血浆炎症因子水平[20]。

3 皮肤粘膜炎症与衰老疾病

皮肤表面分泌抗菌肽抵抗环境微生物感染。老年人的皮肤及粘膜抵抗细菌、病毒感染，防御外伤等保护机能方面明显比年轻人减弱[21]。抗菌肽也是人类非特异性免疫力的一个非炎症反应的组成部分，主要包括 Defensin 和 Cathelicidin 两类，由皮肤粘膜上皮细胞产生，作用是保护皮肤及其它器官组织免受致病微生物侵害[22]。Defensin2 又称防卫素 2，有多个二硫键，很难人工生产，只能通过生物活性透明质酸诱导产生[23,24]。Dale 等[25]报道口腔牙龈粘膜防卫素 2 等抗菌肽分泌水平与口腔牙龈粘膜和牙齿炎症疾病相关，推断防治牙龈炎症疾病有可能成为一种重要的科学养生手段。老年人的口腔牙龈粘膜和牙齿在抵抗细菌、病毒感染，防御外伤等保护机能方面减弱，需要有效的保护[26]。人类消化道总面积与体表面积相似，如有炎症，对衰老影响重大，有证据表明食用非炎症刺激食物和抗炎食物可以减少肠粘膜炎症和降低血浆炎症因子水平[27-29]。

4 溶解臭氧和生物活性透明质酸

杀菌是抗炎的前提，寻找即有杀菌效果又有强大的炎症抑制作用、无痛、可吞咽、无化学残留、除异味和能漂白的口腔牙龈粘膜和牙齿杀菌消炎剂一直是口腔医生的梦想[30,31]。国内外的研究表明[32-35]，溶解臭氧水的符合上述标准，是一种有效的口腔牙龈粘膜和牙齿疾病防治方法，百特和惠士康团队分别研发生产了溶解臭氧水漱口刷牙消毒和家用电器产品，可用来防治口咽牙齿炎症疾病。

生物活性透明质酸可能通过诱导防卫素分泌产生治疗作用。Kapoor 等[36]报道了生物活性透明质酸漱口成功治疗口腔溃疡，Rodrigues 等[37]报道了生物活性透明质酸溶液结合消毒剂漱口有效抑制了牙菌斑生长。Molar 公司研发的 Gengigel 是一种每天使用 2-3 次和每次使用 10 毫升生物活性透明质酸的漱口水，主要用来刺激口腔和咽部组织再生，可能通过促进口腔牙龈粘膜生产抗菌肽，抑制细菌生长和辅助治疗口腔溃疡、牙龈出血、牙龈炎、牙周病、牙龈退缩和咽炎。在国内，安瑞普团队研发生产了 2%生物活性透明质酸漱口液产品，可吞咽，吞咽后生物活性透明质酸还能防止上呼吸道感炎症、消化道炎症、关节炎和增加体内透明质酸含量[38]。

Hill 等[32]报道人初乳中含有高达 0.75 毫克 / 每毫升的生物活性透明质酸，从人初乳中纯化的生物活性透明质酸促进了肠道粘膜细胞生产诱导防卫素 -2，提示生物活性透明质酸可以促进肠道粘膜的防护能力和减少肠粘膜炎症疾病。因此，生物活性透明质酸产品有可能成为有效防止消化道炎症和保护肠道粘膜屏障的一种抗炎食品的临床营养新方法。

我国人口老龄化日趋严重，老年人的皮肤在抵抗细菌、病毒感染，防御外伤等保护机能方面明显比年轻人减弱，需要有效的皮肤保护及炎症防制手段。Gariboldi 等[39]报道生物活性透明质酸诱导了皮肤最表层的角质形成细胞生产诱导防卫素 -2，表明生物活性透明质酸的应用可以促进抗微生物感染和自身防护能力。已有的生物活性透明质酸产品如主要用于治疗皮肤刺激性炎症[40,41]。Schlesinger 和 Powell[42,43]报道了生物活性透明质酸能有效治疗脂溢性皮炎和酒糟鼻，2%生物活性透明质酸抑菌抗炎产品，用于有效防治衰老相关的皮肤炎症。因此，生物活性透明质酸产品是一种有效防止皮肤炎症的科学方法[44]。

Cathelicidin 没有二硫键，容易生产，抗菌和防腐能力强，还有抗炎功效，是新一代皮肤杀菌抗炎药物。最近，中国科学院昆明动物研究所赖仞[45]报道 Cathelicidin 抗菌肽有可能成为一种防止皮肤炎症的科学养生方法。

生物活性透明质酸产品 Ialoclean 鼻腔和口咽喷剂主要用于治疗环境污染和胃酸反流造成的激惹性呛咳和咽炎、口咽手术后粘膜伤口保护、鼻粘膜分泌物过多、环境污染造成的鼻炎和过敏性鼻炎等[46]。因此，开发生产 2%生物活性透明质酸粘膜喷剂产品，喷和滴鼻产品大量使用也是通过鼻腔进入咽部对咽部炎症控制的有效方法。

5 小结与展望

综上所述，生物活性透明质酸产品是一种有效的口腔、鼻

腔、上呼吸道、上消化道粘膜炎症防治方法，有可能成为一种重要的抗衰老相关疾病方法。炎症参与了衰老相关疾病的发生和发展[47]，炎症和衰老紧密相关。生物活性透明质酸的皮肤、阴道上皮、口腔粘膜、牙龈粘膜、眼结膜、上呼吸道粘膜的抗炎产品的普及应用可能是科学养生的重要途径，也是减少人体系统炎症刺激水平的干预方法[48,49]。国内有研究表明，肠道粘膜屏障功能与代谢综合征的炎症病因学说相关[50,51]，提示大剂量生物活性透明质酸口服作为一种控制肠道粘膜屏障炎症和通透性的临床营养食品，可能成为防治代谢综合征降低人类心脑血管炎症疾病的危险因素的新方法。另外，高纯度生物活性透明质酸注射给药也有可能成为减少体内关节和其它无菌炎症的新治疗方法，还可能直接抑制血管内皮炎症和影响血管弹性，这值得我们进一步深入研究。

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