

### 【综述】

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### 2.1 抗血管生成

在肿瘤生长和转移过程中,血管

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生成通过提供营养素、氧和旁分泌的交换来刺激肿瘤而促进肿瘤迅速生长。VEGF 是在血管系统发育过程中最重要的调节因子,通常在乳腺癌中过度表达。绿茶及其有效成分,尤其是 EGCG,能抑制乳腺肿瘤生长、增殖、侵袭及血管生长<sup>[16]</sup>。Luo 等<sup>[17]</sup>研究显示,EGCG 干预可减少血浆中 VEGF 水平,而且使肿瘤微血管生成减少,其机制可能与 EGCG 抑制低氧诱导因子 1 $\alpha$  (hypoxiainducible factor 1 alpha, HIF-1 $\alpha$ )和核因子 kB 的活化相关<sup>[17]</sup>;EGCG 减少人乳腺癌细胞密歇根癌症基金会-7 (Michigan Cancer Eoundation-7, MCF-7)细胞中 HIF-1 $\alpha$  和 VEGF 的表达,并能抑制其生长。因此,抑制 VEGF 转录可能是参与绿茶抗血管生成的一种分子机制。EGCG 还可通过阻滞细胞外信号调节激酶 1/2 抑制 VEGF 的表达抑制血管生成<sup>[18]</sup>。

**2.2 对靶蛋白的作用** EGCG 的 8 个酚基可作为许多生物分子的氢键供体。研究表明,EGCG 以高亲和力与几种靶蛋白结合,包括磷脂酰肌醇 3 激酶<sup>[19]</sup>、67-KDa 层黏素受体<sup>[20]</sup>、鸟苷三磷酸酶激活蛋白 (Src 同源结构域 3) 结合蛋白 1<sup>[21]</sup>、B 淋巴细胞瘤-2<sup>[22]</sup>、波形蛋白<sup>[23]</sup>、葡萄糖调节蛋白 78<sup>[24]</sup>、细胞信号转导分子  $\zeta$  链相关蛋白 70<sup>[25]</sup> 及胰岛素样生长因子受体 1<sup>[26]</sup> 等。这些蛋白质在 EGCG 对人乳腺癌细胞系或动物乳腺癌模型的抑制中起重要作用。

**2.3 对细胞信号传导途径的抑制** 表皮生长因子家族的第 2 成员人类表皮生长因子受体-2 (human epidermal growth receptor 2, Her-2) 在约 30% 的乳腺癌患者中过度表达,并且与患者总生存率有关。EGCG 可减少基质磷酸化和 Her-2 结构的激活<sup>[27]</sup>。另外,有研究表明,EGCG 通过诱导高迁移率族蛋白转录因子 1 转录抑制物,进而阻断 Wnt 信号途径,抑制乳腺癌侵袭。在 DMBA 诱导的小鼠乳腺癌中,EGCG 通过调节 Wnt 诱导信号通路蛋白基因降低了肿瘤负荷和侵袭性,并延长了肿瘤的潜伏期<sup>[28]</sup>。

**2.4 抑制肿瘤细胞增殖和诱导肿瘤细胞凋亡** 细胞增殖和凋亡的失控是癌症的 1 个标志。研究表明,EGCG 可抑制三阴性乳腺癌细胞 Hs587T<sup>[29]</sup>、MDA-MB-231<sup>[30]</sup>、雌激素和孕激素受体阳性乳腺癌细胞<sup>[31]</sup>、Her-2 基因阳性乳腺癌 NF639 细胞<sup>[32]</sup> 等的增殖和生长。Alshatwi 等<sup>[33]</sup> 发现 30  $\mu\text{mol} \cdot \text{L}^{-1}$  的 EGCG 可抑制人乳腺癌细胞系 MCF-7 细胞细胞周期蛋白依赖性激酶 2、4 活性,进而细胞周期阻滞在 G<sub>0</sub> 期和 G<sub>1</sub> 期,EGCG 可增加促进凋亡基因半胱天冬酶 3、8、9 和肿瘤抑制基因 p53 的表达。

**2.5 对微小核糖核酸 (micro messenger ribonucleic acid, miRNA) 的作用** miRNA 是微小的 (约 22 个碱基)、单链内源非编码 RNA,能反向调节 mRNA 的转录和稳定。它能受到 EGCG 作用引起多个分子靶点和路径的微小改变。miRNA27a 直接靶向作用

于叉头状转录因子 1,后者是一种假定的肿瘤抑制物,能调节乳腺癌 MCF-7 细胞内源性蛋白的表达<sup>[34]</sup>。miRNA21 和 miRNA27 在 MCF-7 乳腺癌细胞中超表达,miRNA21 能下调肿瘤抑制基因原肌球蛋白 1,而 EGCG 能下调 miRNA21 和 miRNA27 的表达<sup>[34]</sup>。这些研究均表明,绿茶有效成分调节 miRNA 的表达可能是绿茶发挥抗乳腺癌作用的潜在机制之一。

**2.6 其他可能机制** 研究表明,EGCG 有逆转表观遗传的潜力<sup>[35]</sup>。EGCG 可能通过去甲基化作用逆转雌激素受体阴性的乳腺癌细胞雌激素受体的表达<sup>[36]</sup>。另外,有研究表明,EGCG 能增强 ER 下游基因稳态三叶因子 1 和孕激素的 mRNA 表达水平<sup>[37]</sup>。绿茶及 EGCG 可作为抗癌药物的增敏剂,紫杉醇和 EGCG 结合可协同作用抑制乳腺癌细胞 MDA-MB-231,预示紫杉醇和 EGCG 并装于脂质体内可用于治疗浸润性乳腺癌<sup>[38]</sup>。另外,EGCG 可以干扰乳腺癌患者雌激素受体功能,抑制雌激素介导的乳腺癌细胞增殖,并可提高内分泌药物如他莫西芬的激素敏感性<sup>[39]</sup>。对这些机制中的每一种深入研究将会揭开绿茶在乳腺癌防治方面的更多细节。

### 3 结语

绿茶及其有效成分尤其是 EGCG,可以通过累加或协同效应以及通过减少不良反应来增强传统癌症治疗方法的效果,其机制是多途径、多靶点综合作用的结果。EGCG 在抗乳腺癌方面具有潜在的研究价值,特别是对其抗乳腺癌的细胞分子机制的研究有利于更深层次地了解绿茶及其有效成分 EGCG 的功能效应。有必要对绿茶及其有效成分的抗乳腺癌作用机制以及不同给药途径引起的效应进行深入研究,在获得充分实验依据基础上,可将绿茶及其有效成分研发成为新一代的治疗乳腺癌的药物。

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