NRF2信号通路在乳腺癌中的研究进展

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摘要 乳腺癌已经成为女性最常见的肿瘤之一, 严重危害女性的身心健康甚至危及生命。核因子E2相关因子(nuclear factor erythroid-derived factor 2-related factor, NRF2)主要通过结合靶基因启动子上的抗氧化应答元件(antioxidant response element, ARE)来转录激活下游靶基因的表达, 最近许多研究都表明NRF2在乳腺癌的发展中有着重要作用。该文主要总结了乳腺癌中能通过与NRF2相互作用而对乳腺癌发展产生影响的信号通路, 其中包括蛋白激酶B(protein kinase B, AKT)、P53、信号转导和转录激活因子3(signal transducer and activator of transcription 3, STAT3)等经典信号通路, 同时也阐明了NRF2与microRNA产生的相互作用对乳腺癌发展的影响。由于NRF2在乳腺癌中的重要性, 文章还总结了经典的NRF2激活剂与抑制剂, 这些化合物将来可能在乳腺癌的预防和辅助治疗中发挥重要作用。

关键词 核因子E2相关因子; 乳腺癌; NRF2激活剂

Research Progress on the Role of NRF2 Signaling Pathway in Breast Cancer

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Abstract Breast cancer has become one of the most common tumors in women, seriously endangering women's physical and mental health and even life-threatening. NRF2 (nuclear factor erythroid-derived factor 2-related factor), mainly activates downstream transcription by binding to the ARE (antioxidant response element) on the promoter of the target gene. Many recent studies have shown that NRF2 plays an important role in the development of breast cancer. This article mainly summarizes the signaling pathways in breast cancer that can affect the development of breast cancer by interacting with NRF2, including classic signaling pathways such as protein kinase B (AKT), P53, and STAT3 (signal transducer and activator of transcription 3). It also clarified the influence of the interaction between NRF2 and microRNA on the development of breast cancer. Due to the importance of NRF2 in breast cancer, this article also summarizes the classic NRF2 activators and inhibitors. These compounds may play an important role in the prevention and adjuvant treatment of breast cancer in the future.

Keywords NRF2; breast cancer; NRF2 activators

乳腺癌是目前造成女性癌症死亡的第二大肿瘤类型, 然而乳腺癌的发病机制还没有完全阐明, 目前, 研究发现NRF2与包括乳腺癌在内的多种肿瘤关系密切[1]。NRF2属于转录因子CNC(cap n collar)亚家族一员, 含有高度保守的碱性亮氨酸拉链(basic region-leucine zipper, bZIP)结构, 当细胞面对氧化应

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激时, NRF2入核与抗氧化反应元件(antioxidant response element, ARE)结合后上调抗氧化相关基因的表达[2], 减少正常细胞中的活性氧(reactive oxidative species, ROS)水平, 使细胞维持氧化还原平衡, 抑制肿瘤的发生。NRF2还可与多条信号通路发生串扰, 参与调控多条物质代谢通路, 影响肿瘤细胞的增殖与转移, 同时还与肿瘤耐药有关[3-4]。目前, 许多研究都认为NRF2能通过与多条信号通路发生串扰, 对乳腺癌的发展产生影响, 表明NRF2在乳腺癌的发展过程中具有重要作用。

1 NRF2信号通路简介

NRF2作为一种转录因子, 包括6个高度保守的ECH同源结构域, 即Neh1~6, 其中Neh2含有DLG和ETGE结构。正常情况下, Neh2可与Kelch样ECH相关蛋白1(kelch-like ECH-associated protein 1, Keap1)中的Kelch结构域结合形成复合物[3], 与Cul3-E3泛素连接酶连接, 促进NRF2的泛素化降解, 抑制NRF2从胞质转移到核内。蛋白激酶2(casein kinase 2, CK2)由于能够通过自噬降解keap1, 从而可以保护NRF2免受蛋白酶体降解[5]。而当细胞受到氧化或某些化学因子刺激时, Keap1中的半胱氨酸残基构象改变, 导致NRF2与Keap1分离进入细胞核内, 促进下游抗氧化基因的转录活化[2], 维持细胞内的氧化平衡。含有与NRF2中ETGE或DLG相似的基序的蛋白质, 如选择性自噬接头蛋白p62[6], 二肽基肽酶3(dipeptidyl-peptidase 3, DPP3)[7], 乙型肝炎病毒X蛋白结合蛋白(hepatitis B X-interacting protein, HBXIP)[8], 可以与NRF2竞争结合Keap1, 直接激活NRF2, 维持乳腺癌细胞内的氧化平衡, 起到保护乳腺癌细胞的作用, 对乳腺癌的生长和转移及预后产生影响。

NRF2从细胞质转移至细胞核后, 能与核酸序列上的ARE结合, 启动醌氧化还原酶(quinone Oxidoreductase 1, *NQO1*)、谷氨酸半胱氨酸连接酶(glutamate-cysteine ligase catalytic subunit, *GCLC*)、谷胱甘肽-*S*-转移酶(glutathione-*S*-transferase, *GST*)、血红素加氧酶-1(heme oxygenase-1, *HO-1*)等抗氧化基因的转录[9]。这些基因能够编码II相解毒酶, 促进正常细胞中ROS的清除, 从而抑制乳腺肿瘤的发生, 所以在正常细胞中激活NRF2可以预防肿瘤的发生, 但是癌细胞中ROS的清除也能保护乳腺癌细胞抵抗氧化应激, 导致乳腺癌细胞对化疗药物耐药。其中NQO1与糖代谢相关, 最近的研究表明NQO1通过与*PKLR*(pyruvate kinase liver/red)和*PKM2*(pyruvate kinase M2)等糖代谢相关基因结合, 最终影响乳腺癌的增殖、转移[10-11]。NQO1还与乳腺癌耐药有关, NQO1在乳腺癌细胞中高度表达会导致线粒体氧化代谢、线粒体生物合成的增加, 从而使得乳腺癌细胞对他莫昔芬耐药, 用已知的NQO1抑制剂二氢香豆酚处理乳腺癌细胞后, 他莫昔芬耐药性表型被逆转[12]。

HO-1是血红素分解代谢过程中的限速酶, 可产生一些生物活性分子: 一氧化碳、亚铁离子和胆绿素。一方面, HO-1被诱导激活之后通过促进自噬使乳腺癌细胞对表阿霉素及拉帕替尼等化疗药物耐药[13-14]。另一方面, 体内过表达HO-1能够抑制4T1小鼠模型中肿瘤的肺转移, 其机制是HO-1能通过抑制Notch信号通路和基质金属蛋白酶9(matrix metalloproteinase-9, MMP-9)的激活[15], 抑制乳腺癌的侵袭和转移, 说明HO-1在乳腺癌耐药和转移中起重要作用[16]。

2 与NRF2发生串扰的信号通路

在乳腺癌中, NRF2作为一种转录因子, 其入核后除了能激活靶基因的表达, 还能够通过与许多经典的信号通路发生串扰, 从而对乳腺癌的发生发展产生影响(表1)。

2.1 抑制乳腺肿瘤的发生, 促进乳腺癌的发展

在正常细胞中, BRCA1(breast cancer susceptibility gene-1)、P53等信号通路与NRF2相互作用之后, 会激活NRF2, 减小ROS对正常细胞的损害, 抑制乳腺肿瘤的发生。但是乳腺癌细胞中NRF2的激活也会起到保护癌细胞的作用, 从而促进乳腺癌的发展。

2.1.1 NRF2与BRCA1 乳腺癌1号基因(breast cancer susceptibility gene-1, *BRCA1*), 是一种直接与遗传性乳腺癌有关的抑癌基因, 拥有这个基因的家族与高乳腺癌发生率有关[17]。研究发现, NRF2与组蛋白乙酰转移酶家族主要成员CBP/p300形成活性转录复合物后, 可以与*BRCA1*启动子上的ARE位点结合, 诱导组蛋白乙酰化, 促进*BRCA1*启动子的转录[18]。不仅如此, 在小鼠原代乳腺上皮细胞中, BRCA1蛋白能够通过与NRF2的ETGE区域结合, 抑制NRF2的泛素化降解, 促进NRF2稳定激活, 所以当*BRCA1*基因发生缺失或突变时, NRF2信号通路受到抑制, ROS水平上升, 这可能与乳腺癌的发生有关[19], 并且

表1 NRF2在乳腺癌中的作用及作用机制

Table 1 The role and mechanism of NRF2 in breast cancer

作用 Role	与NRF2串扰的信号通路 Signaling pathway crosstalks with NRF2 signal	作用机制 Action mechanism	参考文献 References
Inhibiting the occurrence of breast cancer and promoting the development of breast cancer	BRCA1 signaling pathway	① BRCA1 can bind to NRF2 to inhibit the ubiquitination and degradation of NRF2 to inhibit tumorigenesis ② When BRCA1 mutation occurs in breast cancer cells, estrogen can compensatory upregulate NRF2 to protect cancer cells from ROS damage	[19-20]
	P53 signaling pathway	① P53 and NRF2 have a synergistic effect. When NRF2 is inhibited, P53 will be activated compensatory, which can inhibit the occurrence and proliferation of breast cancer ② P53 and NRF2 synergistically activate the transcription of proteasome subunit genes and thioredoxin system related genes such as TXN and TXNRD1 to promoe proliferation and metastasis	[21-23]
Promoting the development of breast cancer	AKT signaling pathway	① Mutant AKT (E17K) can inhibit NRF2 degradation to promote glutathione synthesis to promote tumor proliferation	[27]
	HIF-1α signaling pathway	① NRF2 can upregulate the expression of HIF-1α, which can affect tumor metabolism, promote tumor proliferation and metastasis	[29-30]
	RhoA signaling pathway	① NRF2 can regulate RhoA protein degradation and its transcription, which can promote focal adhesion formation to promote migration ② NRF2 can also directly bind to the promoter of RhoA to induce the expression of RhoA to promote migration	[32-33]
	STAT3 signaling pathway	① NRF2 can combine with P-STAT3^{Y705} dimer to form a stable complex to upregulate the expression of IL-23A, which can promote the development of breast cancer	[35]
Inhibiting the development of breast cancer	FPN1 signaling pathway	① NRF2 can promote the transcription and expression of FPN1, facilitate iron transport from cancer cells, which can inhibite tumor proliferation	[39-40]
Producing dual roles	HER2 signaling pathway	① HER2 activation can upregulate the expression of NRF2 to promote breast cancer cell resistance to adriamycin ② HER2 inhibition will change cell metabolism, leading to oxidative stress and compensatory upregulation of NRF2 to induce tumor recurrence ③ NRF2 directly binds to HER2 to inhibit HER2 transcription to inhibite tumor proliferation	[42-44]

此时雌激素能通过调节磷脂酰肌醇-3-激酶/蛋白激酶B (phosphatidyl inositol 3-kinase/protein kinase B, PI3K/AKT)信号通路上调NRF2, 这弥补了*BRCA1*突变所导致的NRF2通路的抑制, 从而保护乳腺癌细胞免受ROS导致的细胞死亡[20]。研究BRCA1与NRF2之间的相互作用对治疗*BRCA1*突变的乳腺癌具有重要意义。

2.1.2 NRF2与P53 *P53*基因是重要的抑癌基因之一, 具有抑制肿瘤的作用, 且超过50%的癌症伴有*P53*基因的突变。在*P53*经常发生突变的三阴性乳腺癌中, P53错义突变体通过其DNA结合域中的aa 98~128与NRF2相互作用, 将NRF2募集到蛋白酶体亚基基因和一些特定基因ARE元件的启动子上, 协同激活蛋白酶体亚单位基因和硫氧还蛋白系统有关的基因如硫氧还蛋白(thioredoxin, *TXN*)、硫氧还蛋白还原酶1(thioredoxin reductase 1, *TXNRD*1)基因的转录, 其中*TXN*的转录激活与乳腺癌的预后不良有关。并且在氧化应激条件下, 突变型P53与NRF2相互作用所产生的生物学效应会对乳腺癌细胞的存活和转移产生影响[21-22]。在正常原发乳腺组织和激素阴性乳腺导管原位癌中, NRF2信号通路受到抑制之后, P53信号通路会被补偿性激活, 使正常细胞能抵抗氧化应激, 起到保护细胞作用。单独抑制其中的一种信号通路对乳腺癌上皮细胞的表型并没有明显

的影响，而当这两种信号通路在乳腺上皮细胞中同时受到干扰时，乳腺上皮细胞会出现明显的ROS依赖性表型，这会影响乳腺正常生长发育和乳腺癌早期生长。在*P53*通常突变的三阴性乳腺癌中，NRF2与P53不具有这种协同作用，单独抑制NRF2不会导致P53的激活而起到保护癌细胞的作用[23]。故NRF2有望成为治疗三阴性乳腺癌的靶点。

2.2 NRF2促进乳腺癌发展

NRF2与蛋白激酶B(protein kinase B, AKT)、缺氧诱导因子-1α(hypoxia inducible factor-1α, HIF-1α)等信号通路发生串扰之后能够促进乳腺癌细胞的增殖和转移，而对乳腺肿瘤的发生不产生影响。

2.2.1 NRF2与AKT 磷脂酰肌醇-3-激酶/蛋白激酶B(phosphatidyl inositol 3-kinase/protein kinase B, PI3K/AKT)信号通路是一条经典的致癌信号通路，可以影响肿瘤的生长增殖和代谢[24]。研究发现，PI3K-AKT也能够促进抗氧化基因的表达，表明NRF2可能与PI3K/AKT信号通路相关[25]。一方面，AKT作为一种丝氨酸/苏氨酸蛋白激酶，在将NRF2磷酸化后，能促进NRF2从胞质向核内转移，所以AKT受到抑制之后会显著降低核NRF2蛋白的表达[26]。另一方面，AKT容易发生E17K突变，即赖氨酸取代17位的谷氨酸，突变的AKT(E17K)能抑制NRF2在细胞质中被降解，促进NRF2稳定激活，使促进谷胱甘肽合成的基因表达增加，让乳腺癌细胞可以抵抗氧化应激、促进肿瘤增殖[27]。用能抑制谷胱甘肽合成的磺胺与顺铂协同作用乳腺癌细胞后，可以选择性诱导PI3K途径突变型乳腺癌细胞的生长，这表明将来可以通过靶向谷胱甘肽的生物合成来治疗PI3K途径突变型乳腺癌。

2.2.2 NRF2与HIF-1α 缺氧诱导因子-1α(hypoxia inducible factor-1α, HIF-1α)是调节氧平衡的关键转录因子，在低氧或某些特定条件下，HIF-1α能从胞质进入细胞核内促进糖酵解相关酶以及磷酸戊糖途径相关酶基因的转录[28]。通过对乳腺癌患者的组织进行分析，发现NRF2与HIF-1α的表达呈正相关，且将乳腺癌细胞株中的NRF2过度表达之后，HIF-1α的表达明显上调，葡萄糖-6-磷酸酶的转录与表达增加，进而上调Notch1信号通路促进乳腺癌细胞的增殖和转移[29-30]。这些研究表明，NRF2可以正向调节HIF1-α来影响肿瘤代谢，促进乳腺癌的发展。NRF2和HIF-1α可以成为治疗乳腺癌的潜在分子靶标。

2.2.3 NRF2与RhoA Ras同源基因家族成员A(ras homolog gene family member A, RhoA)属于Ras超级家族，以结合GDP(无活性)和结合GTP(有活性)的方式发挥重要的分子开关作用。RhoA蛋白是参与细胞增殖、分化、迁移和极性肌动蛋白细胞骨架的调节因子，在肿瘤的增殖和迁移中有重要作用[31]。NRF2通过调控RhoA的蛋白降解和转录表达来对乳腺癌的转移产生影响，NRF2能抑制雌激素相关受体α(estrogen-related receptor alpha, ERRα)介导的RhoA降解，使RhoA以及Rho激酶(Rho kinase, Rock)等RhoA下游信号蛋白的表达增加，促进黏附斑的形成和乳腺癌细胞的迁移[32]。NRF2也可以与RhoA的启动子直接结合，诱导RhoA的表达，化合物YD0514通过抑制NRF2/RhoA/ROCK信号通路，使转移性三阴性乳腺癌异种移植瘤的生长受到抑制[33]。YD0514具有作为转移性乳腺癌的抗癌候选药物的潜力，可以进一步进行临床前和临床方面的研究。

2.2.4 NRF2与STAT3 信号转导和转录激活子3(signal transducer and activator of transcription 3, STAT3)存在于胞质中，可被多种细胞因子或其他胞外信号激活，激活后形成二聚体进入细胞核中与靶DNA序列结合，具有信号转导和转录调控双重功能。利用NRF2-ome数据库预测了STAT3和NRF2信号通路之间有相互作用的可能性[34]。在基底样乳腺癌中，STAT3的酪氨酸705位点容易发生磷酸化形成P-STAT3^{Y705}二聚体使STAT3活化，研究发现NRF2能够与P-STAT3^{Y705}二聚体结合形成稳定的复合物，这种复合物与白细胞介素23A(interleukin 23A, *IL23A*)基因的启动子结合，转录上调IL23A的表达来加速基底型乳腺癌的发展[35]。这表明STAT3和NRF2有成为治疗基底样乳腺癌新型靶标的潜力。

2.3 NRF2抑制乳腺癌的发展

膜铁转运蛋白1(ferroportin1, FPN1)是一种铁转运蛋白，主要负责系统性铁的供应、利用、回收和储存，而铁作为机体必需的营养元素参与多种生命过程，其代谢平衡对于维护细胞正常功能和机体的健康至关重要，Hepcidin-FPN1轴主要负责维持全身铁稳态[36]，Hepcidin-FPN信号通路的异常会增加肿瘤发生和肿瘤恶化的风险[37]。用NRF2激动剂莱菔硫烷处理乳腺癌细胞能上调小鼠巨噬细胞中*FPN1* mRNA，表明NRF2可通过促进*FPN1*基因转录控制炎症过程中的铁代谢[38]，NRF2也可以与前列腺癌细胞和乳腺癌细胞中的*FPN1*启动子结合来促进*FPN1*的转录和表达，

有利于铁从癌细胞运出, 使铁的致瘤作用减弱, 进而抑制癌细胞的生长[39-40]。这些研究都表明, NRF2对FPN1的调控在肿瘤中发挥着至关重要的作用。

2.4 NRF2产生抑制和促进乳腺癌发展的双重作用

在乳腺癌患者中通常可以发现人类表皮生长因子受体2(human epidermal growth factor 2, *HER2*)基因的扩增和过表达, 乳腺癌中15%~20%的乳腺癌患者呈HER2阳性[41]。研究发现, 当HER2被激活后, HER2与NRF2直接结合, 促进NRF2和其靶蛋白的表达, 使乳腺癌细胞对阿霉素产生耐药性[42]。乳腺癌细胞中HER2的下调会促进细胞代谢的变化, 最终导致氧化应激和NRF2的代偿性上调, 促进氧化还原稳态和核苷酸代谢使休眠期肿瘤的复发[43]。而另一项研究则发现, 用NRF2的激动剂姜黄素处理乳腺癌细胞株之后, *HER2*的mRNA水平显著下降, NRF2通过与*HER2*启动子直接结合抑制*HER2*的转录, 进而抑制乳腺癌细胞的增殖[44]。这表明影响NRF2与HER2之间的相互作用可能是治疗乳腺癌的新策略。

3 microRNA与NRF2信号通路的作用

miRNA(microRNA)是一种小的非编码RNA分子, 包含20~25个核苷酸, 它们通过与mRNA的3′-非翻译区(3′-UTR)完全或部分结合而负调控靶基因的表达。NRF2能被许多miRNAs靶向, 其中miR-144-3p[45]、miR-634[46]可直接与NRF2的3′-UTR区结合抑制NRF2的转录, 促进癌细胞对化疗药物的敏感性。而miR-155则可以通过直接激活NRF2信号通路使肺癌细胞对三氧化二砷耐药[47]。此外, miRNAs还可以通过靶向Keap1来激活NRF2, 如miR-432-3p[48]可以直接与Keap1的编码区结合下调Keap1的表达, 使NRF2稳定激活, 抑制癌细胞对顺铂的化学敏感性, 而miR-141则是靶向Keap1的3′-UTR促进*Keap1* mRNA的降解, 激活NRF2信号通路, 从而显著抑制由5-氟尿嘧啶介导的细胞毒性[49]。这说明NRF2与microRNA之间的相互作用对癌症的发展有重要影响。

在乳腺癌中, NRF2也与microRNA关系密切。一方面, microRNA能通过调控NRF2来调节致癌过程, 在雌激素诱导的乳腺癌中, 雌激素能诱导miR-93激活, miR-93通过转录后调控其靶基因*NRF2*的表达[50]。而miR-28则通过靶向*NRF2* mRNA的3′-UTR, 降低NRF2的表达[51]。另一方面, NRF2也能通过调节microRNA影响乳腺癌细胞的生长, 其中miR-29b-1-5p在受到NRF2的调控之后会发挥其对细胞的保护作用[26]。同时研究发现, *NRF2*的敲低可以提高miR-181c水平, 从而抑制缺氧状态下HIF-1α介导的适应性代谢改变[52]。这些研究结果表明, NRF2能通过与多种miRNAs产生相互作用影响乳腺癌的发展, 再次表明了NRF2在乳腺癌中的重要作用。

4 乳腺癌中靶向NRF2的化合物

由于NRF2在乳腺癌发生发展中的重要作用, NRF2有望成为乳腺癌预防和治疗的新靶点。近些年, 从植物中分离提取的许多化合物能与NRF2产生相互作用, 这些化合物有望在乳腺癌的预防与辅助治疗中发挥重要作用。这里总结了NRF2经典的激活剂和抑制剂在乳腺癌中的作用。

4.1 NRF2激活剂

因为正常细胞中NRF2的激活可以有效减少ROS对正常细胞的损害, 从而抑制乳腺肿瘤的发生, 所以未来NRF2的激活剂或许可以在乳腺癌的预防和辅助治疗中发挥作用。

4.1.1 *白藜芦醇* 研究发现用白藜芦醇处理二甲基苯并蒽诱导的模型大鼠后, 白藜芦醇可以通过激活NRF2促进人乳腺上皮细胞中雌激素的代谢, 抑制乳腺肿瘤的发生, 延长肿瘤的潜伏期[53]。同时白藜芦醇可以通过逆转雌激素介导的*NRF2*启动子的甲基化, 诱导NRF2的激活。用白藜芦醇处理雌性ACI大鼠模型, 可降低模型大鼠中乳腺肿瘤发生率并延长雌激素诱导的乳腺肿瘤的潜伏期[54]。这些研究结果表明, 白藜芦醇可以通过激活NRF2的表达来抑制雌激素引起的乳腺癌变, 它将来能够在乳腺癌的预防与辅助治疗中发挥重要的作用。

4.1.2 *白术内酯II* 白术内酯II通过c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK)/细胞外调节蛋白激酶(extracellular regulated protein kinase, ERK)-NRF2-ARE通路来增强NRF2及其下游解毒酶的表达, 从而抑制雌激素诱导的MCF10A细胞的恶性转化。用白术内酯II处理*N*-亚硝基-*N*-甲基脲诱导的模型大鼠后, 肿瘤的发生率和肿瘤的体积显著下降, 并能抑制大鼠乳腺组织的炎症及氧化应激反应[55]。白术内酯II有望成为乳腺癌的新型化学预防药物。

4.1.3 *莱菔硫烷* 阿霉素可用于治疗早期或淋巴结阳性乳腺癌以及HER2阳性的乳腺癌, 但是有较

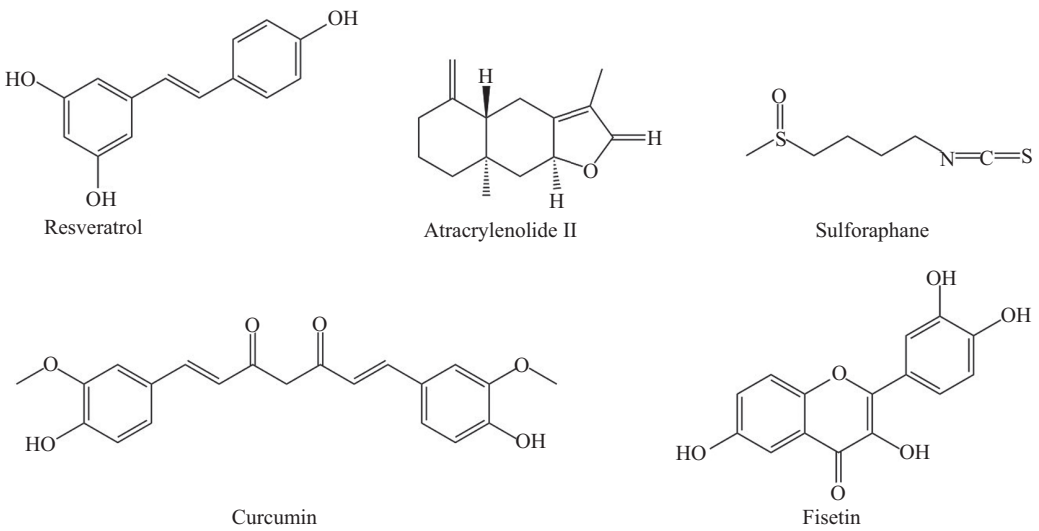

图1 NRF2激活剂

Fig.1 NRF2 activators

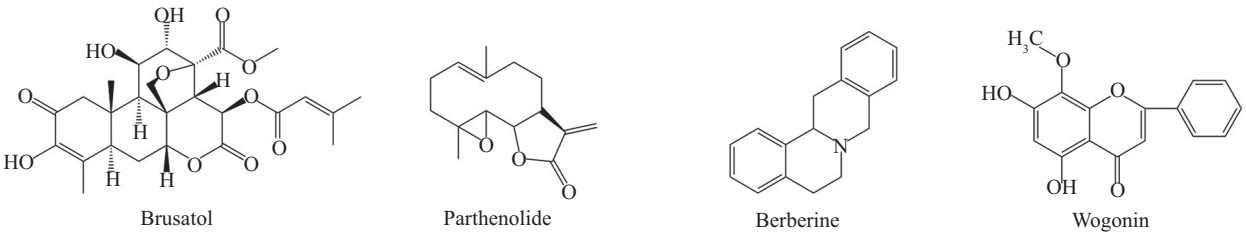

图2 NRF2抑制剂

Fig.2 NRF2 inhibitors

强的心脏毒性, 研究发现, 当莱菔硫烷与阿霉素联用处理乳腺癌模型小鼠后, 莱菔硫烷通过激活心脏中NRF2上调解毒途径, 从而减轻阿霉素引起的心脏毒性[56]。所以当用阿霉素治疗乳腺癌时, 莱菔硫烷可能可以作为有效的心脏保护剂, 减轻阿霉素对乳腺癌患者的副作用。

已开发出大多数已知的NRF2激活剂能通过靶向NRF2, 抑制乳腺癌的发生发展。其中, 白术内酯II和白藜芦醇已经被证明。在体内外对乳腺癌的发生有预防作用, 这两种药物可能成为新型的乳腺癌的化学预防剂。还有些化合物如姜黄素[57]和绯瑟酮[58]激活NRF2后, 能在体外抑制乳腺癌细胞的增殖和转移, 这两个化合物虽未进行体内研究, 但是仍有成为乳腺癌治疗的辅助药物的可能(图1)。

4.2 NRF2抑制剂

乳腺癌细胞中NRF2的激活, 会保护乳腺癌细胞抵抗氧化应激, 从而使乳腺癌细胞对化疗药物耐药。所以NRF2的抑制剂或许可以克服临床上乳腺癌耐药的问题。

NRF2的抑制剂如鸦胆子苦醇[59]、小白菊内酯[60]、黄连素[61]和汉黄芩素[62]通过下调NRF2的表达, 可以促使乳腺癌细胞对阿霉素、拉帕替尼、米托蒽醌等化疗药物敏感, 抑制乳腺癌细胞的生长。但是近几年来这些NRF2抑制剂在乳腺癌中的研究大部分都停留在体外, 需要通过体内和临床实验进一步验证这些化合物的作用, 从而在临床上解决乳腺癌对化疗药物耐药的问题(图2)。

目前大多数的NRF2激活剂和抑制剂都具有其他分子靶标, 未来应着重开发更具特异性的NRF2靶向化合物。

5 小结和展望

乳腺癌是女性最常见的恶性肿瘤之一, 许多研究发现NRF2信号通路能够通过与乳腺癌细胞中PI3K信号通路、P53信号通路、STAT3信号通路等一些关键信号通路及microRNA发生相互作用来影响乳腺癌的发展。针对NRF2在乳腺癌中的作用, NRF2信号通路可以作为乳腺癌预防和治疗的潜在

靶点, 研究发现, 许多NRF2的激活剂如莱菔硫烷、白藜芦醇、白术内酯II等对体外和体内乳腺癌模型都显示出预防与治疗作用, 但是这些化合物在乳腺癌中的研究都停留在临床前, 还需要进一步进行临床方面的研究, 并且很多作用于NRF2的化合物都不具有很强的特异性, 因此发现特异性靶向NRF2的化合物是十分重要的。相信随着对NRF2与乳腺癌相互关系的进一步深入研究, NRF2将为探讨乳腺癌的发病机制及乳腺癌的临床生物治疗开辟新的途径。

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