多糖调控p53信号网络研究进展

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摘要 肿瘤抑制基因*p53*是目前研究最广泛和系统的抑癌基因之一。*p53*与其上、下游基因形成复杂的信号网络来发挥功能。*p53*基因的突变或缺失与多种人类恶性肿瘤的发生、发展密切相关, 所以*p53*基因是目前多种抗肿瘤药物开发的靶点。多糖由于其低毒和抗肿瘤效果成为生物大分子抗肿瘤的研究热点。目前认为, 多糖在体内外抗肿瘤机制有两方面: 一是通过增强机体免疫力以抑制肿瘤增殖, 另一则是激活胞内信号通路, 调控肿瘤相关基因表达, 诱导肿瘤细胞衰老、细胞周期阻滞与凋亡达到对肿瘤细胞的抑制作用。该文综述了近些年多糖通过调控p53信号网络来发挥其抗肿瘤及抗衰老等作用, 为多糖的开发与利用提供参考依据。

关键词 多糖; p53信号网络; 调控; 生物活性

Progress of Polysaccharides Regulating p53 Signal Network

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Abstract *p53* is one of the most extensive and systematic cancer suppressor genes and its function-related genes consists of a complicated gene network. The mutation and deletion of the *p53* gene is highly associated with the development of human malignancies, so *p53* gene is a target for the developments of the anti-cancer drugs. Polysaccharides are attracted more attention on antitumor drug screening with having low side effects. The polysaccharides are enhancing the immunity and regulated the intracellular signaling pathways to achieve its anti-tumor activity. We summarized the research advance of antitumor mechanism of polysaccharides through the regulation of p53 signal network, which provided some basis for the development and utilization of polysaccharides for the future studies.

Keywords polysaccharides; p53 signal network; regulation; biological activity

多糖(polysaccharides)广泛存在于动物、植物和微生物中, 是由多个单糖分子通过糖苷键连接而成的多聚物。多糖是构成生命的四大基本物质之一, 其分子结构复杂且庞大。多糖低毒且有显著的生物活性(如: 抗肿瘤、抗衰老及神经保护作用等), 被中外学者广泛研究。已有很多关于多糖抗肿瘤分子机制中通过激活胞内信号通路调控肿瘤相关基因表达从而诱导肿瘤细胞的细胞周期阻滞与凋亡的研究, 多糖对p53信号网络的调控便属于其中之一。关于多糖通过调控肿瘤相关基因进而诱导肿瘤细胞的细胞周期阻滞与凋亡的研究已有很多, 其中包括多糖对p53信号网络的调控。本文主要综述了近些年国内外有关多糖通过调控p53信号网络来发挥其功能的研究。

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1 p53信号网络

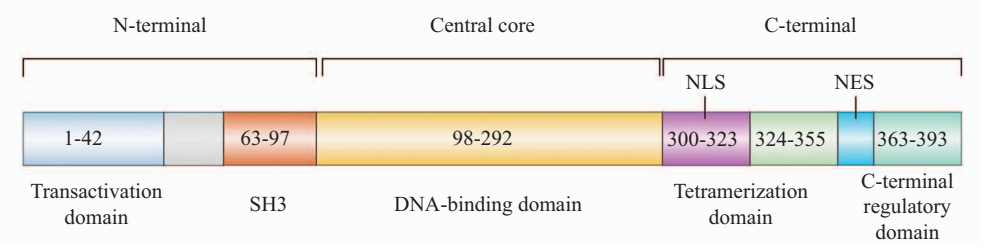
人类*p53*基因定位于17号染色体(短臂, 17p13), 含11个外显子, 在人类癌症中这一区域经常发生突

变, 野生型*p53*基因编码的蛋白质包含393个氨基酸, 通常可以分为三个功能域(图1)。酸性激活结构域对转录激活是必需的, 这一区域也负责与各种转录因子的相互作用。MDM2(murine double minute 2)可以与p53的N-端转录激活结构域相互作用来抑制p53的转录活性[1]。多数情况下, p53与其靶蛋白的相互作用发生在p53中央核心的序列特异性DNA结合结构域。p53的C-端包含四聚结构域、一个核输出信号和一个核定位信号[2]。在C-端的最末端由许多碱性氨基酸组成, 主要调节中央DNA结合结构域, 这一区域是p53发生突变最常见的区域, 其次是四聚结构域(3.4%)、脯氨酸富集结构域(2.3%)、转录激活结构域(1%)和调节性C-端(0.3%)[3], 这些突变大多是错义突变(73%)。

在超过50%的癌症类型中*p53*基因均发生突变, 这使p53信号通路失去细胞生长“制动器”的功能[4]。野生型p53蛋白质位于调节细胞生长与死亡信号网络的交叉点, 对细胞生长、分化、衰老、应激和凋亡等生命过程起着决定作用, 同时, 它与胞内其他信号通路也存在着错综复杂的关系[5]。因此, Vogelstein等[6]认为, 不能单独衡量p53的生物学功能, 应将其上游、中游和下游的相关基因联系起来形成体系, 这些体系之间错综复杂的相互作用才是调节生命活动的根本, 即p53信号网络(图2)。

1.1　p53上游激活信号网络

正常情况下, 细胞内野生型p53蛋白质在胞内的浓度受到转录水平、翻译水平及翻译后修饰水平、胞内亚细胞定位水平等多方面的精细立体调节, 其水平被维持在极低状态, p53信号网络处于关闭状态。当细胞经受应激或损伤时, p53被稳定并积累, 发挥其损伤细胞生长“制动器”功能, 清除受损DNA和突变细胞, 防止癌症的发生。能够激活p53信号网

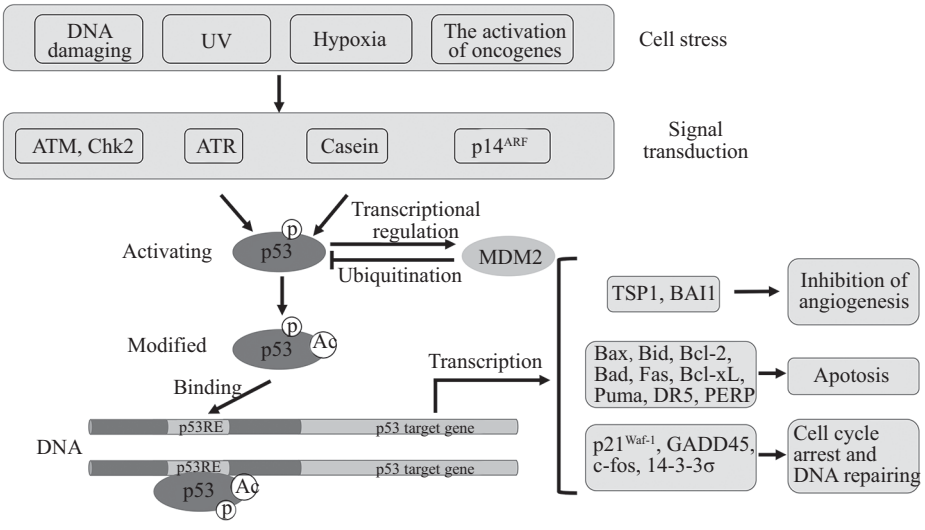


NES: 核输出信号; NLS: 核定位信号。

NES: nuclear export signals; NLS: nuclear localization signals

图1　p53的功能结构域(根据参考文献[17]修改)

Fig.1　Functional domains of p53 (modified from reference [17])



Chk2: 细胞周期检查点激酶2; Casein: 酪蛋白; Ac: 乙酰化; p: 磷酸化; TSP1: 血小板反应素; BAI1: 脑组织特异性抑制因子1。

Chk2: cell cycle checkpoint kinase 2; Ac: acetylation; p: phosphorylation; TSP1: thrombospondin 1; BAI1: brain-specific angiogenesis inhibitor 1.

图2　*p53*基因调控网络

Fig.2　The regulation network of *p53* gene

络的上游信号包括: 紫外线(ultraviolet, UV)和电离辐射引起的DNA损伤、原癌基因异常活化、缺氧应激等。

上述激活信号多是产生细胞损伤和突变, 为防止损伤或突变细胞积累, p53信号网络被激活。其中, DNA损伤的原因有很多, 如UV照射、化疗和电离辐射等。不同的DNA损伤类型会激活不同的下游信号, 如分别响应于电离辐射和UV照射的ATM(ataxia telangiectasia-mutated)和ATR(ATM and Rad3-related), 它们是磷脂酰肌醇-3-激酶样激酶家族(phosphateidylinositol-3-kinase-like kinases, PIKKs)成员, 能启动一系列磷酸化反应, 最终都会导致p53在胞内稳定并积累[11-13]。原癌基因激活以及缺氧应激等也能通过一系列磷酸化反应将信号传递给p53, 最终抑制p53的降解, 使p53在胞内维持较高水平并发挥功能。

1.2 p53中游调控网络

相比于p53蛋白质的生成速度, p53的降解速度对机体内野生型p53在胞内水平的调控更加重要, 负责调控p53在胞内水平最为经典的途径就是p53与MDM2的负反馈调节机制。p53是一种动态的分子, 主要在细胞核内发挥功能, 所以p53的活性很大程度上被其亚细胞定位决定着, p53通过C-端自身的核定位信号(nuclear localization signals, NLS)定位于核内, 而人类MDM2含有一个核输出序列(nuclear export signals, NES), 可以介导其自身或者结合到该序列上的异源蛋白质由细胞核向胞质的运输[14]。所以, 机体在正常情况下, p53与MDM2相互结合, MDM2捕获p53并介导其穿过核膜进入胞质, 进入胞质的p53随即被泛素化而降解, 使核内p53维持在极低的水平。由于p53分子中的MDM2结合区与自身转录激活区(transactivation domain, TAD)相重叠, 所以MDM2与p53的结合使p53丧失了与转录蛋白结合的能力, 从而抑制了p53转录激活活性。此外, *MDM2*还是p53转录的靶基因, p53转录可以增加核内MDM2的浓度, 高表达的MDM2会与p53结合形成复合物, 这一负反馈调节机制严格控制了p53在胞内的浓度。然而, MDM2过表达, 则会影响应激条件下p53在胞内浓度, 使p53即使在应激条件下也无法达到发挥功能的浓度, 导致损伤DNA积累, 突变细胞无法及时被清除而形成肿瘤, 这也是*MDM2*被称为癌基因的原因[15]。

研究还发现, $p14^{ARF}$蛋白质能与MDM2结合, 阻碍MDM2介导的p53的亚细胞定位及泛素化降解, 从而提高胞内p53的浓度, 但$p14^{ARF}$与MDM2的结合并不影响p53与MDM2的结合。除上述机制外, p53在胞内还受到共价修饰的调控[16], 包括磷酸化、乙酰化、糖基化和泛素化等。这些翻译后修饰对p53在胞内的稳定与积累是必需的。研究表明, p53的磷酸化修饰更多的是阻碍p53向胞质中的转运, 从而减少p53的降解, 增加p53的稳定性, 而乙酰化修饰则是增加p53的转录活性[17]。正是如此多维立体因素的相互制约与平衡, 才能实现p53在胞内适时地扮演着“基因组卫士”的角色[18]。

1.3 p53下游功能网络

p53在胞内的作用主要是介导DNA损伤后细胞的应激反应, 如诱导细胞周期阻滞、促进DNA修复和受损细胞凋亡, 从而避免损伤DNA片段的积累, 维持基因组的稳定。p53作用于下游数量众多、功能各异的靶基因来发挥作用。

1.3.1 p53介导的细胞周期阻滞 细胞防止DNA损伤积累的机制是细胞周期检查点, 至少有两个检查点在细胞周期进程推进过程中发挥重要作用。G_1期检查点决定G_1期向S期的推进, 使机体有时间检查DNA是否发生损伤, 避免受损DNA进入复制。G_2期检查点决定G_2期向M期的推进, 从而避免受损DNA进入有丝分裂。p53激活引起的细胞G_1期阻滞主要是通过激活p53下游靶基因*p21*, 即周期依赖性激酶抑制剂来实现的。一方面, p21可以与cyclin CDK复合物结合, 抑制相应的蛋白激酶活性, 阻止Rb蛋白的磷酸化, 损伤细胞无法通过G_1期检查点而使机体有时间对受损细胞作出反应。此外, p21还可与PCNA(proliferating cell nuclear antigen)结合, 阻断DNA复制。有研究表明, 这一过程中组蛋白乙酰化酶抑制剂对p53的C-端373/382位点赖氨酸的乙酰化是很重要的[19]。p53的另外3个下游基因*cyclin B1*、*gadd45*和*14-3-3σ*则参与G_2/M期阻滞。细胞周期的及时阻滞可以使受损DNA修复, 让细胞“评估”自己的受损程度, 进而决定细胞的“命运”, 如无法修复则会诱导细胞凋亡, 具体通过何种机制让细胞作出“决定”目前并不清楚[20]。

1.3.2 p53介导的细胞凋亡 一旦细胞受损过于严重, p53就可以通过激活线粒体途径和死亡受体途径导致caspase家族活化, 从而介导细胞凋亡。线

粒体途径主要是通过调节p53效应器Bcl-2(B-cell lymphoma-2)蛋白质家族, 如Bax(Bcl-2-associated X)[21-22]和PUMA(p53 up-regulated modulator of apotosis)[23]。死亡受体途径, p53可以诱导死亡受体Fas(TNF receptor superfamily member 6)和DR5(death receptor 5)的表达[24], 而且还可诱导TRAIL(TNF related apoptosis inducing ligand)和Fas L(Fas ligand)的表达[25]。最近的研究表明, EPSIN 3是p53的一个新靶点, 在调控凋亡通路和胃癌发生过程中发挥重要作用[26]。

1.3.3　*其他功能*　除上述作用外, p53还可参与DNA修复过程, 其DNA结合结构域本身具有核酸内切酶的活性, 可切除错配核苷酸, 调控DNA的修复。同时, p53还可诱导细胞衰老[27]以及抑制肿瘤血管生成。肿瘤生长到一定程度后, 可通过自分泌途径形成促血管生成因子, 刺激营养血管在瘤体实质内增生。p53蛋白质能刺激血管生成抑制基因*Smad4*[Smad蛋白的一词来源于果蝇(*Drosophila*) mothers against dpp(Mad)和*C. elegans*(线虫)的Small(Sma)蛋白, dpp(decapentaplegic)是骨形成蛋白BMP的同源物]、*TSP1*(thrombospondin 1)及*BAI1*(brain-specific angiogenesis inhibitor 1)等表达, 抑制肿瘤组织的血管生成, 切断肿瘤组织的"养料"供给, 抑制肿瘤的生长。

2　多糖对p53信号网络的调控

根据来源不同, 多糖可分为动物多糖、植物多糖和微生物多糖。由于多糖具有良好的生物活性且低毒的特点, 近年来受到科研工作者的广泛关注。明确多糖的抗肿瘤机制对多糖的合理开发与应用非常重要。目前有研究发现, 多糖能够通过调控p53信号网络来发挥其抗肿瘤和抗衰老等生物活性。

2.1　动物多糖对p53信号网络的调控作用

动物多糖种类繁多, 在动物体内分布广泛。动物多糖的抗肿瘤等生物活性也被广泛研究, Suo等[28]研究发现, 大黄鱼鱼鳔多糖能激活人结肠癌HCT-116细胞的p53信号网络, 上调p53信号网络中p53、Bax、p21、Apaf-1、caspase-3、caspase-8、caspase-9、Fas mRNA及蛋白质水平, 下调Bcl-2、Bcl-xL和Fas L mRNA及蛋白质水平, 从而诱导HCT-116细胞凋亡。泥鳅多糖同样能上调SMMC-7721的*p53*和*Bax*的mRNA水平, 降低Bcl-2/Bax比率, 达到抗肿瘤效果[29]。河蚬多糖和泥螺多糖都能够通过上调p53蛋白质水平来诱导肿瘤细胞的周期阻滞和细胞凋亡[30]。海参硫酸多糖同样能调控p53信号网络, 只不过是通过关闭p53信号网络, 下调由6-羟基多巴胺(6-hydroxydopamine, 6-OHDA)诱导的p-p53、cleaved-caspase-3、cleaved-caspase-9和Bax蛋白质水平, 从而缓解了6-OHDA以及缺氧应激引起的细胞毒性[31-32]。研究发现, 海参硫酸多糖是通过抑制MAPK信号通路并激活NF-κB、PI3K(phosphoinositide 3-kinase)/AKT(protein kinase)信号通路来转导应激信号, 并最终激活p53信号网络来发挥作用[31]。

2.2　植物多糖对p53信号网络的调控作用

植物中的糖类占干重的80%以上, 参与植物的各种生理代谢, 具有广泛的药理活性。目前认为, 多糖是通过受体激活了胞内信号通路, 从而发挥药理活性。表1总结了植物多糖对p53信号网络的调控作用。

p53位于细胞生长、死亡与应激等信号的交叉点, 正常情况下维持在极低水平, 当细胞经受应激时, p53信号网络被激活。表1中归芪多糖等能够下调氧化应激、辐射引起的p53信号网络的过度活化, 从而缓解由于应激引起的p53信号网络过度活化而产生的损伤。*p53*基因在人类大约50%的癌症中都存在突变, 突变后的*p53*不但失去了其原有功能, 在许多癌症中还可能会获得一系列癌基因特性的功能, 而猕猴桃多糖能够下调突变型p53蛋白质水平, 关闭异常p53信号网络, 抑制移植瘤生长。五味子多糖、海藻多糖、枸杞多糖以及鼎湖鳞伞多糖等则能通过激活HSP90(heat shock protein 90)/PI3K/AKT、AMPK(adenosine 5′-monophosphate (AMP)-activated protein kinase)及ERK(extracellular regulated protein kinases)等上游信号通路, 将细胞应激转导至p53, 从而激活p53信号网络, 诱导肿瘤细胞凋亡。不同种类多糖能通过不同的上游信号通路, 将应激信号转导到胞内p53信号通路上, 而p53则会根据应激信号类型, 启动下游基因转录等, 从而产生相应的生物学效应。

2.3　微生物多糖对p53信号网络的调控作用

微生物多糖来源广泛, 生产周期短且多数可再生, 是国内外研究与应用较多的一类多糖。在微生物多糖中, 真菌多糖由于其较好的抗肿瘤、抗氧化、

表1 植物多糖对p53信号网络的调控作用

Table 1 The effect of plant polysaccharides regulating p53 signal network

多糖 Polysaccharide	作用细胞系 Cell line	调控网络 Regulatory network	作用机制 Mechanism
Boschniakia rossica polysaccharide (BRP)[33]	HepG2 cell line (N)	Up-regulated the expression of Bax and p53 proteins and down-regulated the expression of Bcl-2 protein	Induced cancer cell apoptosis
Fructus *Schisandra chinensis* (Turz.) baill polysaccharide[34]	HepG2 cell line (N)	Up-regulated the expression of Bax and p53 proteins and down-regulated the expression of Bcl-2 protein	Induced cancer cell apoptosis through Hsp90/AKT signalling pathway
Red wine polysaccharide[35]	Walker-256 tumor-bearing rats (N)	Up-regulated the expression of p53 proteins	Induced cancer cell apoptosis through p53 signalling pathway
Panax ginseng polysaccharide (APG)[36]	C57BL/6 mouse small intestine (N)	Up-regulated the expression of Bax and p53 proteins and down-regulated the expression of Bcl-2 and Bcl-xL protein	APG protects the mouse small intestine from irradiation-induced apoptosis through inhibition of the p53-dependent pathway
Pyracantha fortuneana polysaccharides[37]	MDA-MB-231 breast cancer cells (Y)	Up-regulated the expression of p53, Puma and Noxa protein	Induced cancer cell apoptosis
Curcuma kwangsiensis polysaccharides[38]	CNE-2 human nasopharyngeal carcinoma cells (Y)	Up-regulated the expression of p53 proteins and down-regulated the expression of Bcl-2 protein	Induced cancer cell apoptosis
Tarphochlamys affinis polysaccharide[39]	H22 tumor-bearing mice (Y)	Up-regulated the expression of Bax and p53 proteins and down-regulated the expression of Bcl-2 protein	Induced H22 cell apoptosis
Cactus polysaccharides[40]	Lung squamous carcinoma cells (Y)	Up-regulated the expression of p53 proteins	Induced cancer cell cycle arrest and apotosis
Schisandra chinensis polysaccharide (SCP)[41]	Renal cell carcinoma model (N)	Up-regulated the expression of Bax and p53 proteins and down-regulated the expression of Bcl-2 protein	Inhibition of tumor angiogenesis
Glycyrrhiza polysaccharide(GPS)[42]	Human hepatocellular carcinoma cells (Y)	Up-regulated the expression of p53 proteins and *p53* mRNA	Induced cancer cell apoptosis
Pholiota dinghuensis Bi polysaccharide (PDP)[43]	Human breast cancer cells (Y)	Up-regulated the expression of Bax, p21 and p-p53 proteins and down-regulated the expression of Bcl-2 protein	Induced human breast cancer cell apoptosis
Safflower polysaccharide[44]	MCF-7 cell line (N)	Up-regulated the expression of Bax and p53 proteins and down-regulated the expression of Bcl-2 protein	Induced human breast cancer cell apoptosis
Apple pectin[45]	Mouse bearing 4T1 cancer tumors (N)	Up-regulated the expression of p53 proteins	Induced cancer cell apoptosis
Algae extract polysaccharide[46]	Human gastric carcinoma MKN45 cells (N)	Up-regulated the expression of p53, caspase-3, caspase-9 protein	Induced Human gastric carcinoma MKN45 cells apoptosis
Guiqi polysaccharide (GOP)[47]	Human fetal lung fibroblast WI-38 cells (N)	GQP significantly affected the p53-p21 and p16-pRb pathways in H_2O_2-treated WI-38 cells	GQP has protective effects in oxidative stress-induced senescence
Pectin[48]	Octylphenol (OP) induced oxidative stress, renal injury in mice (N)	Up-regulated OP induced the decrease of p53 proteins and down-regulated the expression of Bcl-2 protein	Pectin has antioxidant and anti-apoptotic activities in kidney toxicity induced by OP
Sargassum integerrimum polysaccharide[49]	A549 cell line (N)	Up-regulated the expression of Bax and p53 proteins and down-regulated the expression of Bcl-2 protein	Induced A549 cells apoptosis
Astragalus polysaccharide (APS)[50]	Non-small cell lung carcinoma cell lines (N)	Up-regulated the expression of Bax, p21 and p53 proteins and down-regulated the expression of Bcl-2 protein	Induced cancer cell apoptosis
Sulfated polysaccharide[51]	Human hepatoma HLF cell line (N)	Up-regulated the expression of p53 proteins and phosphorylation of AMPK protein	Sulfated polysaccharide inhibits proliferation through G_1/S transition in HLF cells
Dictyophora indusiata polysaccharide[52]	S180 cells (N)	Up-regulated the expression of CDK4 and p53 proteins and down-regulated the expression of Bcl-2 protein	Induced S180 cell apoptosis
Actinidia chinensis polysaccharide[53]	Orthotopic transplanted cancer of gastric tumor in 615 mice (Y)	Down-regulated the expression of mutant p53 protein	Inhibit the growth of orthotopic transplanted cancer of gastric tumor in 615 mice
Actinidia chinensis polysaccharide[54]	MCF-7 cell line (N)	Up-regulated the expression of p21, p-p53 and p53 protein	Induced MCF-7 cell apoptosis

表中作用细胞系后字母N表示*p53*基因未突变, Y表示*p53*基因已经发生突变。

The letters in the table behind the cell line, N represent that the *p53* gene is normal in this cell line, Y represent that the *p53* gene has been mutated in this cell line.

表2　真菌多糖对p53信号网络的调控作用

Table 2　The effect of Fungal polysaccharides regulating p53 signal network

多糖 Polysaccharide	作用细胞系 Cell line	调控网络 Regulatory network	作用机制 Mechanism
Nostoc commune vauch polysaccharide[55]	MCF-7 cell line (N)	Up-regulated the expression of Bax and p53 proteins and down-regulated the expression of Bcl-2 protein	Induced MCF-7 cell apoptosis
Pyropolyporus fomentaries sporophore polysaccharide[56]	S180 cells line (N)	Down-regulated the expression of mutant p53 protein	Induced S180 cell apoptosis
Polyporus umbellatus polysaccharide[57]	MCF-7 cell line (N)	Up-regulated the expression of p53 proteins	Induced MCF-7 cell apoptosis
Hericium erinaceus polysaccharide (HEG-5)[58]	SGC-7901 cell line (N)	Up-regulated the expression of CDK4, Bax and p53 proteins and down-regulated the expression of Bcl-2 protein	Induced cancer cell cycle arrest and apotosis
Lentinus edodes polysaccharide (JLNT)[59]	Mouse sarcoma S180 cells and human breast cancer MCF-7 cell lines (N)	Up-regulated the expression of caspase-3, Bax and p53 proteins and down-regulated the expression of Bcl-2 protein	Induced cancer cell apoptosis
Ganoderma atrum polysaccharide (PSG-1)[60]	CT26 mouse colon cell line (N)	Up-regulated the expression of Bax and p53 proteins and down-regulated the expression of Bcl-2 protein	Induced CT-26 cell apoptosis
Auricularia polytricha polysaccharides (APPs)[61]	A549 cell line (N)	Up-regulated the expression of p53 protein	Induced A549 cell cycle arrest and apotosis
Pleurotus abalonus acidic polysaccharides[62]	MCF-7 cell line (N)	Up-regulated the expression of p53 and apotosis proteins	Induced MCF-7 cell cycle arrest and apotosis
Lactobacillus brevis-*fermented Ecklonia cava* polysaccharide[63]	Primary splenocytes cell (N)	VLFEP markedly reduced the increase of p53 due to γ-ray-irradiation	VLFEP has radioprotective properties through reduced the expression of p53
Trichoderma pseudokoningii exopolysaccharide[64]	Human leukemia K562 cells (N)	Up-regulated the expression of Bax and p53 proteins and down-regulated the expression of Bcl-2 protein	Induced K562 cell apoptosis
Ganoderma lucidum polysaccharides[65]	Human leukemia THP-1 cells (Y)	Up-regulated the expression of p53 protein	Induced THP-1 cell apoptosis

表中作用细胞系后字母N表示*p53*基因未突变, Y表示*p53*基因已经发生突变。

The letters in the table behind the cell line, N represent that the *p53* gene is normal in this cell line, Y represent that the *p53* gene has been mutated in this cell line.

降血脂、免疫调节等生物活性深受研究者们的关注。表2总结了近些年通过调控p53信号网络发挥其抗肿瘤等作用的真菌多糖。

近年来, 微生物多糖由于其低细胞毒性、来源广泛方便且抗肿瘤效果显著等特点引起人们关注。关于真菌多糖的药用开发正在进行, 如云芝多糖、香菇多糖以及茯苓多糖等已临床用于治疗肿瘤。药用真菌多糖开发的第一步就是要明确作用机制。p53作为各类细胞应激信号转导交叉点, 在机体应对应激过程中发挥重要作用。AKT作为响应胞外信号促进生长和存活的信号转导通路, 通过磷酸化一系列胞内蛋白质, 活化其介导的下游反应如: 细胞生长、存活、增殖、迁移和血管生成等, 所以, AKT在许多癌症类型中都发挥重要作用。p53作为AKT下游的靶蛋白, 会执行AKT的部分功能。表2中Tan等[57]发现, 在乳腺癌MCF-7细胞系中, p-AKT高表达, 而猪苓多糖和si-RNA(AKT)处理MCF-7细胞后, p-AKT和p53表达下调, p-p53、PTEN、p21蛋白质水平上调, 同时, 猪苓多糖能够抑制MCF-7细胞活力以及细胞迁移, 并诱导细胞周期阻滞, 最终达到抗肿瘤作

用。由于辐射等应激条件的存在, p53信号网络有时会过度激活, p53信号网络的过度激活同样会对正常细胞产生损伤。短乳杆菌多糖能够通过抑制γ射线引起的NF-κB信号通路的过度激活, 来抑制p53信号通路的过度激活, 从而减弱γ射线对正常脾细胞的辐射损伤。毛木耳多糖、黑灵芝多糖、香菇多糖及松茸多糖等能够激活p53信号网络, 上调促凋亡基因如*Bax*、*Bad*(Bcl-2/Bcl-xL-associated death promoter)、cleaved-caspase3等的表达, 下调抗凋亡基因如*Bcl-2*、*Bcl-xL*(B-cell lymphoma-xL)等的表达, 活化线粒体途径, 诱导肿瘤细胞的周期阻滞与凋亡。

3 存在的问题与展望

多糖作为筛选新型抗肿瘤药物的资源, 可以通过调控p53信号网络诱导肿瘤细胞的细胞周期阻滞和细胞凋亡, 从而达到抗肿瘤的目的, 具有良好的应用前景。但是, 目前在多糖抗肿瘤作用中, 关于多糖调控p53信号网络的研究多集中在p53信号网络的中下游。至于多糖是如何将信号转导至胞内、刺激并稳定p53, 从而发挥作用的研究鲜有报道。同时, 由于多糖本身的复杂性如分离纯化无统一标准、结构复杂以及活性受诸多因素影响等, 给多糖的系统研究和进一步开发药用带来很大困难。因此, 继续加强对多糖的研究、阐明多糖抗肿瘤机制以及其如何激活p53信号网络, 对更好地开发和利用多糖具有重要意义。

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