SPOP在肿瘤发生中的作用

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摘要 SPOP(speckle type BTB/POZ protein)是E3泛素连接酶接头蛋白, *SPOP*的缺失或突变通常引发包括肿瘤在内的多种疾病。迄今为止, 已经报道多种肿瘤的发生发展与*SPOP*基因的缺失或突变有关。SPOP发挥的功能具有组织特异性, SPOP主要通过泛素–蛋白酶体途径降解促进肿瘤生长、侵袭和转移等过程的蛋白, 从而在前列腺癌、子宫内膜癌和乳腺癌中发挥抑癌基因的作用。该文讨论了SPOP在不同组织来源肿瘤的进展过程中的作用及其作用机制。

关键词 SPOP; 肿瘤发生; 抑癌基因; 泛素化

The Role of SPOP in Tumorigenesis

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Abstract SPOP (speckle type BTB/POZ protein) is an E3 ubiquitin ligase adaptor protein. Genomic loss or mutation of *SPOP* locus generally leads to various diseases including tumors. It has been reported that occurrence and development of various types of cancers are closely associated with functional loss or mutation of *SPOP*. However, SPOP functions in a tissue-specific manner. SPOP targets its substrate proteins for proteasomal degradation, and these proteins are usually required for tumor growth, invasion and metastasis. *SPOP* mainly acts as a tumor suppressor gene in prostate cancer, endometrial cancer and breast cancer. Here we summarize recent studies to discuss the role of SPOP and its possible mechanisms in tumor progression in different tissues.

Keywords SPOP; tumorigenesis; tumor suppressor; ubiquitination

泛素–蛋白酶体途径负责调控细胞内多数蛋白的稳态平衡(proteostasis), 在维持蛋白质体内正常生理功能中起着重要作用[1]。泛素–蛋白酶体复合物组分或其底物在遗传上发生改变均会导致蛋白质稳态失衡, 最终引发肿瘤在内的多种疾病[2]。Cul3(Cullin3)是研究最广泛的泛素–蛋白酶体途径组分之一, 而SPOP(speckle type BTB/POZ protein)蛋白是Cul3的一种重要接头蛋白。通过招募和降解不同靶蛋白, SPOP在前列腺癌和子宫内膜癌等肿瘤的发生发展进程中发挥了重要作用[3]。本文就SPOP的一些最新研究进展, 尝试讨论SPOP在多种肿瘤中的作用及其作用机制, 以及一些悬而未决的问题。

1 SPOP蛋白的结构

SPOP含有靠近N-端的MATH(meprin and tumor necrosis factor receptor associated factor homology)结构域和靠近C-端的BTB(bric-a-brac, tramtrack and broad complex)结构域、BACK(BTB and C-terminal kelch)结构域和核定位序列(图1)。其中, MATH结构域主要负责识别并结合靶蛋白; BTB结构域主

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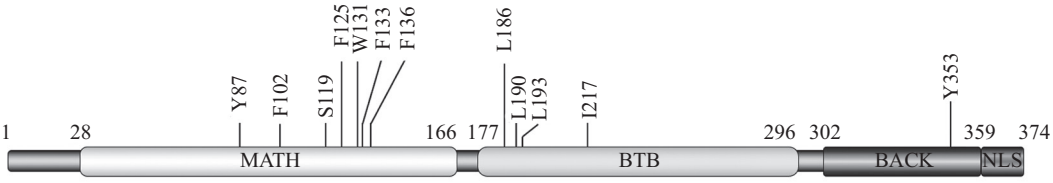

图1 SPOP蛋白结构示意图

Fig.1 Schematic representation of SPOP protein

要负责结合Cul3 E3泛素连接酶, 随后形成SPOP-Cul3-Rbx1 E3泛素连接酶复合物[2,4]。SPOP蛋白通过MATH结构域和BTB结构域介导靶蛋白发生泛素化, 从而调控靶蛋白经26S蛋白酶体途径降解[5]。BTB结构域有助于SPOP形成二聚体, 其中4个氨基酸残基(L186、L190、L193、I217)起重要作用。BACK结构域有助于SPOP形成寡聚体, 其中Y353起重要作用(图1)。BTB结构域与它紧邻的BACK结构域共同参与SPOP单体形成寡聚体, 而SPOP形成寡聚体与发挥正常功能密切相关。SPOP形成寡聚体后能有效促进靶蛋白的泛素化[6], 而不能形成寡聚体的SPOP依旧能与靶蛋白及Cul3结合, 但靶蛋白泛素化明显减少。此外, SPOP通过C-端核定位序列, 通常定位于细胞核[7]。

2 SPOP蛋白的功能

SPOP/Cul3主要功能是负责细胞内的泛素化修饰, 进而调控靶蛋白的定位或稳定性, 而SPOP靶蛋白涉及多种重要的细胞功能(表1)。实际上, SPOP的功能主要取决于靶蛋白的功能, 包括调控器官发育、抑癌作用、促癌作用及其他。例如, BRD4(bromodomain-containing protein 4)是SPOP的一种底物, 其主要作为转录共激活因子在多种细胞过程(包括细胞周期调控、增殖、凋亡、癌细胞迁移与侵袭等)中起关键作用[8]。BRD4可以促进C-Myc[9]等转录因子表达, 且能与P-TEFb(positive transcription elongation factor b)[10]、p53[11]、AR(androgen receptor)[12]等转录延伸因子或转录因子相互作用从而促进下游基因表达。SPOP介导BRD4降解抑制相关转录因子活性和相关基因表达, 这是SPOP调控基因表达的一种方式。另外, SPOP结合靶蛋白并改变部分靶蛋白的亚细胞定位, 这类靶蛋白可能不经历蛋白水解的过程, 如参与X染色体失活的MacroH2A[3]。

SPOP MATH结构域中包含的多个特征性氨基酸残基(图1)促进SPOP与靶蛋白的结合[4]。癌相关SPOP突变体(特征性氨基酸发生点突变)不能结合靶蛋白, 导致SPOP功能缺失, 从而促进癌症的发生发展[13-15]。靶蛋白通过SBC(SPOP-binding consensus)模体——Φ-π-S-S/T-S/T(其中Φ代表非极性氨基酸残基, π代表极性氨基酸残基)与SPOP结合[16], 抑制SBC模体磷酸化的点突变会干扰靶蛋白与SPOP的结合。近些年来, 越来越多的研究结果从多方面阐述了SPOP在调控肿瘤发生发展中的作用。

3 SPOP与前列腺癌

前列腺癌患者的全基因组及外显子测序表明, *SPOP*是前列腺癌中点突变频率最高的基因之一, 且突变位点都集中在MATH结构域上(图1)。在原发性前列腺癌中, *SPOP*突变率为6%~13%, 在转移性前列腺癌中, *SPOP*突变率高达14.5%[17-18]。SPOP可能在癌症形成早期就发生突变, 其突变是前列腺癌发生发展的潜在驱动因子。*SPOP*突变与前列腺癌中频发的*TMPRSS2-ERG*(transmembrane protease serine 2-erythroblast transformation specific related gene)基因重排遗传事件互斥[19-20]。目前研究证明, SPOP抑制前列腺癌的发生发展, 突变或敲除*SPOP*致使小鼠罹患前列腺癌[21-22], 敲低*SPOP*或过表达*SPOP*会提高前列腺癌细胞的侵袭能力[18]。

SPOP靶蛋白大多是原癌基因产物(表1), 其中有10多种是前列腺癌中SPOP的底物。SPOP最经典的靶蛋白是AR, AR在正常前列腺细胞的生长发育和前列腺癌的发生发展中起着重要作用。AR含有与SPOP结合的SBC模体, 而SPOP介导AR的泛素化与降解[13]。SPOP还可以通过介导SRC3(steroid receptor co-activator-3)或TRIM24(tripartite motif-containing 24)降解来抑制AR的转录活性[14]。前列腺癌相关SPOP突

变体不能与AR结合, 也不能介导其降解[13]。雄激素抑制剂促进SPOP介导的AR降解, 而雄激素反之, 核受体超家族蛋白(如糖皮质激素受体)与抗雄激素抗性相关[46]。目前治疗前列腺癌的方法主要是通过阻断AR, 在治疗一段时间后, 多数患者会从AR依赖型前列腺癌转变成去势抵抗型前列腺癌, 但这种转变的机制尚不明确。

BRD4也是SPOP在前列腺癌中的重要靶蛋白之一, 且在前列腺癌中高表达[33]。BRD4是一种广泛的转录共激活因子, 通过上调原癌基因的表达促进癌症的发展。在前列腺癌中, SPOP与BRD4的SBC模体结合, 介导其发生泛素化并降解, 过表达前列腺癌相关的SPOP突变体(如F133V)导致BRD4蛋白水平显著升高, 而缺失SBC模体的BRD4不会被SPOP降解[15,32]。JQ1(triphenylmethane-4,4',4''-triisocyanate)可以抑制BRD4的活性[47], 但是前列腺癌对JQ1有耐药性[33]。野生型SPOP使前列腺癌对JQ1敏感, 而功能缺失型SPOP突变体使前列腺癌对JQ1不敏感[15]。这

表1 SPOP蛋白的底物与功能分类

Table 1 Substrate and function classification of SPOP protein

SPOP的功能 Function of SPOP	底物 Substrate	SPOP底物的功能 Function of SPOP substrate	参考文献 Reference
Organ development regulation	PDX1	Transcription factor required for pancreas development	[24]
	Gli2/3	Transcription factors regulating hedgehog signaling and embryonic development	[25]
	Daxx	Transcription corepressor inhibiting apoptosis	[26]
Tumor suppressor role	SRC3	Transcription coactivator in hormone receptor signaling	[15]
	AR	Transcription factor required for AR signaling	[14]
	DEK	Oncoprotein implicated in epigenetic and transcriptional regulation	[17]
	ERG	Transcription factor regulating proliferation and apoptosis	[20-21]
	SENP7	SUMO-specific proteases inhibiting senescence	[27]
	TRIM24	Oncogenic transcription coactivator and ubiquitin ligase regulating proliferation and apoptosis	[17]
	EglN2	Prolyl hydroxylase regulating hypoxia tolerance and apoptosis	[28]
	Cyclin E1	Regulatory subunit of CDK2 required for cell cycle transition	[29]
	ATF2	Transcriptional activator involved in anti-apoptosis, cell growth, and DNA damage response	[30]
	NANOG	Transcriptional factor maintaining pluripotency of stem cells	[31]
	C-Myc	Transcription factor involved in cell-cycle regulation	[23]
	INF2	Polymerization and depolymerization of actin filaments	[32]
	BRD4	Oncogenic transcription coactivator	[16,33-34]
	Cdc20	Cell-cycle regulation	[35]
	ERα	Transcription factor required for ER signaling	[36]
	BRMS1	Transcriptional repressor inhibiting metastasis	[37]
	HDAC6	Histone deacetylase and transcriptional repressor	[38]
	SIRT2	Transcription regulation, metabolism, DNA repair	[39]
	FADD	Apoptotic adaptor protein	[40]
	DDIT3	Multifunctional transcription factor in ER stress response	[41]
	PR	Transcription factor required for PR signaling	[42]
	PD-L1	Immune inhibitory receptor ligand	[43]
	MMP2	ECM regulation	[44]
Oncogenic role	PTEN	Phosphatase in PI3K signaling pathway	[8]
	DUSP7	Phosphatase in MAP kinase pathway	[8]
Others	MacroH2A	X-inactivation	[3]
	BMI1	Oncogenic transcriptional repressor	[3]
	PIPKIIβ	Phosphatidylinositol phosphate kinase regulating phosphoinositide signaling	[45]
	SETD2	Histone methyltransferase implicated as a tumor suppressor	[46]

可能是由于*SPOP*突变导致其下游基因表达均上调, 促进了前列腺癌对JQ1的耐药性。另外, 前列腺癌对Cdc20(cell division cycle 20 homolog)抑制剂Apcin的耐药性也与SPOP突变有关[34]。由此可见, SPOP突变可以作为前列腺癌治疗效果的一个预后指标, 同时也表明SPOP在协同治疗前列腺癌中的重要作用。

前列腺癌中常发遗传事件是*ETS*(erythroblast transformation-specific/external transcribed spacer)基因重排, 导致ERG蛋白水平上调[48], 从而促进前列腺癌细胞的迁移和侵袭。一直以来, 鲜有研究报道ERG融合蛋白是如何在翻译后水平被调控的。研究揭示, SPOP与ERG在功能上存在联系[19-20]。他们发现, SPOP介导ERG蛋白的泛素化及降解, 并确定ERG蛋白中的SBC模体为氨基端$_{42}$ASSSS$_{46}$序列。前列腺癌相关SPOP突变体不能识别并结合ERG蛋白, 而*TMPRSS2-ERG*融合基因产物(如TMPRSS2-ERGΔ99或TMPRSS2-ERGΔ39)因缺失SBC模体也不能被SPOP蛋白识别。这些证据表明, SPOP可能在翻译后水平调控ERG蛋白水平, 而*SPOP*突变与*ERG*基因重排事件互斥可能是由于功能冗余所致。但是, 最近研究表明, 绝大多数携带*SPOP*突变的前列腺癌患者样本中都不表达ERG蛋白; 同时使用*SPOP*突变型前列腺癌的小鼠模型发现, 前列腺癌相关*SPOP*突变体的表达并不会引起ERG蛋白的过量表达, 也没有发现*ERG*靶基因被异常激活的证据[49]。因此, 前列腺癌中*SPOP*突变和*ERG*激活之间的关联尚需进一步验证。

SPOP调控PD-L1(programmed cell death protein-ligand 1)的表达。PD-L1(一种跨膜蛋白)作为PD-1(programmed cell death protein 1)的配体, 是一种重要的“免疫检查点”蛋白, 表达PD-L1蛋白的癌细胞可以逃避T细胞的杀伤。靶向PD-1和PD-L1的免疫疗法可以治疗多种类型的癌症[50-51], 但是仍有众多癌症患者对靶向PD-1和PD-L1的免疫疗法没有响应[52]。ZHANG等[42]发现, 野生型SPOP结合PD-L1的羧基端(283-290), 介导PD-L1的泛素化及降解, 而前列腺癌相关*SPOP*突变(如F102C)不能介导PD-L1的降解。此外, CDK4(cyclin-dependent kinase 4)通过磷酸化SPOP-S6促进14-3-3γ与SPOP的结合, 而14-3-3γ与SPOP结合可以避免SPOP蛋白被Cdh1(CDC20 homolog 1)介导的泛素化途径降解; 使用CDK4的抑制剂(Palbociclib)与PD-1抗体共同处理多种肿瘤细胞异种移植的小鼠模型发现, 二者联用极大阻碍肿瘤进展且显著提高小鼠的生存率, 这为那些不响应靶向PD-1和PD-L1免疫疗法的癌症患者提供了一种治疗的新思路。然而一个有待回答的问题是, 核定位的SPOP如何与细胞膜跨膜蛋白PD-L1结合? 是SPOP出核并结合到PD-L1上, 还是PD-L1入核并被SPOP调控, 抑或通过其他方式?

部分靶蛋白经SPOP泛素化并不发生蛋白降解, 而是改变亚细胞定位, INF2(formin protein inverted formin 2)即属于这类靶蛋白。INF2可以介导肌动蛋白(actin)在内质网与线粒体交汇处聚集并促进线粒体相关DRP1(dynamin-related protein 1)斑点的形成, 这是线粒体分裂的关键步骤[53]。SPOP通过识别并结合INF2羧基端SBC模体, 介导INF2形成非典型泛素化, 这不会使INF2发生蛋白降解, 而是减少INF2在内质网定位及线粒体中DRP1聚集的量, 最终阻断线粒体分裂。过表达前列腺癌相关*SPOP*突变不能介导INF2泛素化, 但干扰内源性SPOP的功能, 从而促进线粒体的分裂, 最终增强前列腺癌细胞的迁移和侵袭的能力[31]。这代表着SPOP的另一种功能, 即改变其靶蛋白的亚细胞定位。这种功能也为理解癌症发生机制和寻找癌症治疗策略引入一种新观点。

SPOP不仅可以通过调控相关癌蛋白的表达水平或定位, 还可以通过维持基因组稳定来抑制前列腺癌的发生发展。研究表明, SPOP参与了DNA损伤应答, 是维持基因组稳定的重要因子之一[54]。在前列腺癌中, *SPOP*基因突变能引起多种关键的DNA损伤应答因子, 如RAD51(DNA repair protein RAD51 homolog)表达下调, 从而导致基因组不稳定, 诱发癌症发生发展[55-56]。综上所述, SPOP主要通过介导靶蛋白降解或改变靶蛋白亚细胞定位, 在前列腺癌的发生发展中发挥抑癌因子的作用; 另外, SPOP也可以通过维持基因组稳定来抑制前列腺癌的发生发展。前列腺癌相关*SPOP*突变功能的恢复以及与其他靶向药物联用可能是未来治疗前列腺癌的一个方向。

4 SPOP与肾透明细胞癌

SPOP在大多数癌症中是抑癌因子, 但在肾透明细胞癌(clear cell renal cell carcinoma, ccRCC)中是促癌因子[7]。SPOP在99%的ccRCC细胞中高表达[57], 且没有肾癌相关*SPOP*突变的报道。在ccRCC细胞中,

低氧压力和低氧诱导因子(hypoxia-inducible factors, HIFs)促进SPOP高表达并诱导SPOP在细胞质中定位和积累, 从而介导抑癌因子PTEN(phosphatase and tensin homolog)和DUSP7(dual specificity phosphatase 7)的蛋白降解, 促进肿瘤的发生发展[7]。在ccRCC细胞中敲低、敲除*SPOP*基因或抑制SPOP蛋白表达, 均能诱导ccRCC细胞发生凋亡[58], 提示SPOP是ccRCC的潜在靶向位点。基于SPOP在ccRCC中促进肿瘤发生的作用, GUO等[59]进一步开发SPOP小分子抑制剂, 该抑制剂通过干扰SPOP与底物PTEN(phosphatase and tensin homolog)和DUSP7的结合, 而抑制肿瘤生长。另有研究发现, SPOP是上皮间质细胞转化(epithelial-mesenchymal transition, EMT)的激活剂, SPOP主要通过激活β-catenin/TCF4(transcription factor 4)/ZEB1(zinc-finger E-box binding homeobox 1)轴促进EMT相关基因的转录, 从而促进ccRCC的侵袭等过程[60]。因此, SPOP表达水平或其突变与原发性肿瘤的组织来源有关, SPOP在肿瘤发生发展中的作用具有组织特异性。

5 SPOP与子宫内膜癌和乳腺癌

在子宫内膜癌中, 经常发生*SPOP*基因突变, 突变率为5.7%~10.0%[61]。子宫内膜癌相关*SPOP*突变不能介导ERα(estrogen receptor α)蛋白降解, 而野生型SPOP则参与雌激素诱导的ERα降解[61], 这提示, *SPOP*突变导致激素失调进而诱发肿瘤形成。*SPOP*基因点突变频率较高的是前列腺癌和子宫内膜癌, SPOP在这两种癌症中发生突变的结构域相同, 但突变位点及其突变效应完全不同[4]。在前列腺癌中, SPOP突变体(如W131G或F133L)不能结合BET(bromodomain and extra-terminal)蛋白(主要是BRD4), 导致BET蛋白家族的蛋白水平显著提高, 最终引发SPOP突变型前列腺癌患者对BET蛋白抑制剂产生耐药性。但在子宫内膜癌中, SPOP突变体(如E50K、R121Q)结合BET蛋白(主要是BRD3)的能力比野生型SPOP更强, 增强了对BET蛋白的泛素化作用, 促进了BET蛋白降解, 使子宫内膜癌细胞对BET蛋白抑制剂更加敏感[33,62]。这些结果提示, 即使同一蛋白质的同一结构域中发生的不同突变也会引起相反的药敏性, 从而影响治疗效果。

在乳腺癌中, SPOP通过介导PR(progesterone receptor)、SRC3和BRMS1(breast cancer metastasis suppressor 1)等蛋白降解, 抑制乳腺癌细胞的增殖和迁移[36,41,63]。SRC3蛋白是ERα活化的关键性调控因子, 并且在乳腺癌中高表达。SPOP以磷酸化依赖的方式与SRC3相互作用, 促进其降解; 从而抑制其介导的致瘤信号, 阻止肿瘤的发生, 因此SPOP是乳腺癌的抑癌因子[63]。对乳腺癌*SPOP*基因组位点的系统性分析表明, *SPOP*基因拷贝数明显减少[63], 提示在乳腺癌中造成SPOP功能缺失的原因可能不是发生点突变, 而是由于基因组中*SPOP*位点的丢失, 从而导致SPOP蛋白表达水平的下降。

6 SPOP与消化系统恶性肿瘤

SPOP可以抑制胃癌、肝癌及结直肠癌的发生发展。SPOP在胃癌患者样本中表达下调[64], Hedgehog信号通路主要的激活因子Gli2(glioma-associated oncogene homolog family zinc finger protein 2)在胃癌中是SPOP的底物之一[65]。胃癌中表达上调的miR-543可以通过抑制SPOP表达促进胃癌细胞的迁移和侵袭, 另外miR-543还可以诱导胃癌细胞的EMT[66]。在原发性肝癌中, SPOP的表达水平显著下调, 低水平SPOP表达与肝癌患者的不良预后密切相关[67]。SPOP可以抑制肝癌细胞的增殖和迁移, 主要是由于SPOP介导SENP7(SUMO1/sentrin specific peptidase 7)的降解[67]。SPOP在20%~62%的结直肠癌中表达下调[2]。在结直肠癌中, Gli2、HDAC6(histone deacetylase 6)及MMP2(matrix metalloproteinase 2)都是SPOP的靶蛋白, SPOP介导它们降解可分别导致抑制Hedgehog信号通路激活和解除组蛋白乙酰化酶对抑癌基因的转录抑制作用等[37,43,68]。与前列腺癌和子宫内膜癌不同的是, 在消化系统恶性肿瘤中, *SPOP*很少发生体细胞突变[69], 但SPOP的表达下调同样导致SPOP的功能缺失。SPOP表达下调可能与其表观遗传沉默有关, 正如胃癌中miR-543可以抑制*SPOP* mRNA的翻译, 但我们仍不清楚相关的具体机制。

7 SPOP与其他恶性肿瘤

非小细胞肺癌(non-small cell lung cancer, NSCLC)是一类致死率高、治愈率低的恶性肿瘤, 研究发现, NSCLC组织中, SPOP mRNA和蛋白表达水平均显著下调[70]。在NSCLC中NAD^+-依赖型脱乙酰酶SIRT2(silent information regulator 2)高表达, 而SPOP介导SIRT2的降解, 从而抑制NSCLC细胞生长和增殖[38]。

另一个在NSCLC中高表达且由SPOP介导从而被降解的蛋白是FADD(Fas-associating protein with a novel death domain)[39]。另外, 在*SPOP*启动子的CpG岛上发现高甲基化的现象, 这主要是由C/EBPα-SPOP信号通路调控的[71], DNA甲基化导致SPOP转录水平显著下调; 同时, 在NSCLC细胞中, 某些miRNA(如miR-520b)的上调导致*SPOP* mRNA降解从而使SPOP蛋白水平显著降低[72]。这些研究结果揭示, SPOP是NSCLC的潜在治疗靶标。

神经胶质瘤是中枢神经系统中最常见的恶性肿瘤之一[73]。与邻近的正常组织相比, SPOP在神经胶质瘤患者样本中表达下调, SPOP表达上调能抑制实验培养条件下的神经胶质瘤细胞的迁移能力[74]。Hedgehog信号通路可能促进神经胶质瘤的发生发展, 而Hedgehog信号通路中最主要的转录因子Gli2/Gli3是SPOP的底物之一[75]。但目前我们对SPOP在神经胶质瘤发生发展中的具体机制知之甚少, 需要作进一步的研究。

8 结语和展望

SPOP是一种常见的泛素连接酶接头蛋白, SPOP靶蛋白参与多种重要的细胞功能, 而SPOP通过介导靶蛋白的稳定性参与癌症形成(图2)。SPOP在绝大多数癌症中是抑癌因子, 而在肾透明细胞癌中是促癌因子; *SPOP*作为抑癌基因时可分为2种, 在前列腺癌和子宫内膜癌等中主要发生功能缺失性

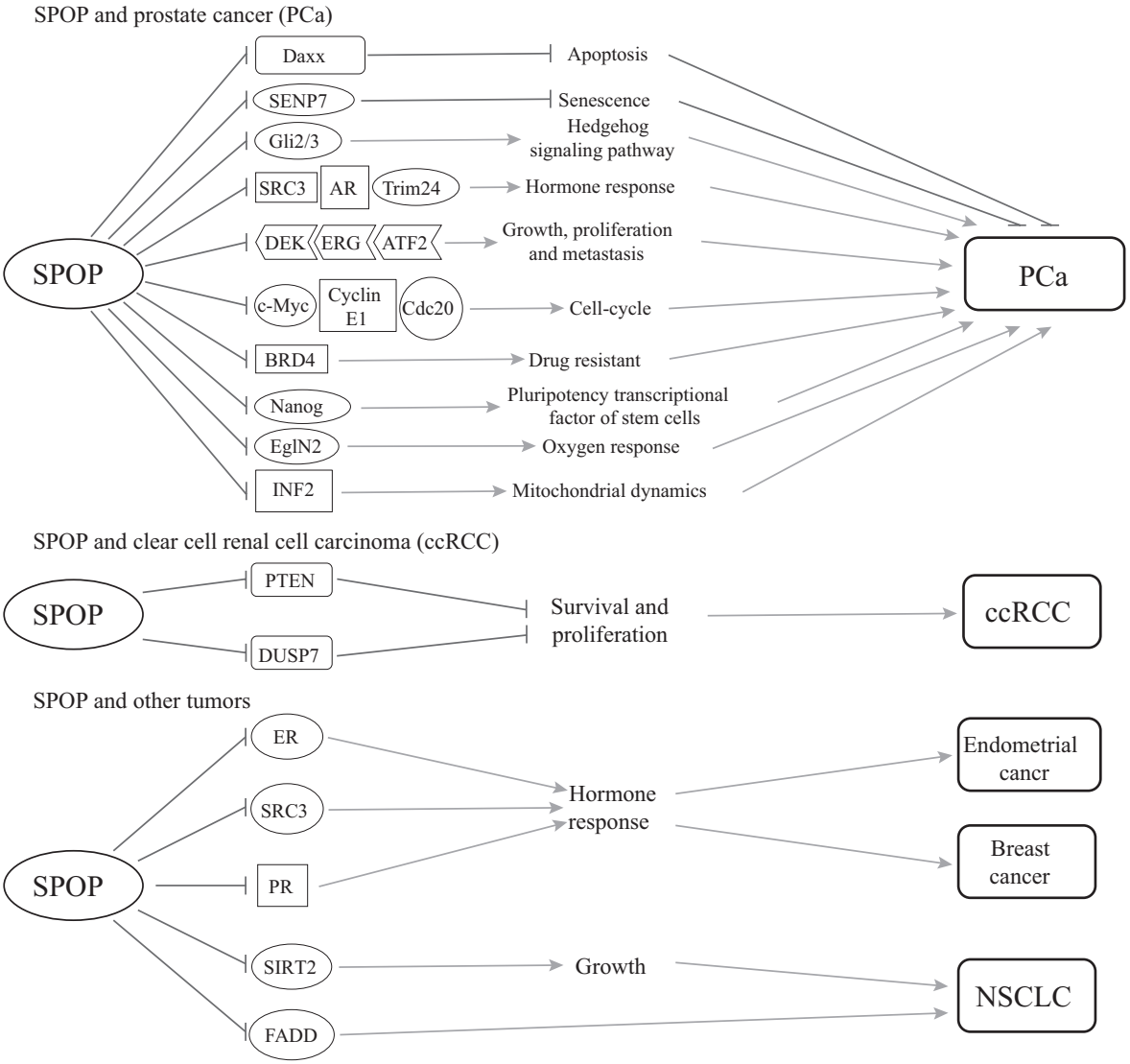

图2 SPOP通过降解不同底物或改变亚细胞定位来调控多种胞内信号通路及相关癌症

Fig.2 SPOP targets multiple substrates for proteasomal degradation or subcellular translocation to regulate different cellular pathways and tumorigenesis

突变, 在其他癌症中主要是由于*SPOP*基因缺失或其mRNA被降解导致蛋白水平显著下调。相比于SPOP基因拷贝数的减少和蛋白表达的下降, SPOP的众多点突变在不同组织中导致的生理病理效应可能更为复杂(如SPOP突变引起前列腺癌和子宫内膜癌对BET蛋白抑制剂的药敏性截然相反)。未来可能需要利用基因编辑等技术建立合适的突变模型来进一步了解SPOP及其突变介导癌症发生发展的分子机制, 并针对SPOP底物以及SPOP的不同点突变开发新的靶向性药物。

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