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TGF-β信号通路在发育和疾病中的调控

孙宏瑶[1], 魏思璇[2], 郗乔然[1*]

1. 清华大学生命科学学院, 教育部蛋白质科学重点实验室, 分子肿瘤学全国重点实验室, 北京 100084;
2. 清华大学生命联合中心, 北京 100084
* 联系人, E-mail: xiqiaoran@mail.tsinghua.edu.cn

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摘要 转化生长因子-β(transforming growth factor-β, TGF-β)信号通路在后生动物胚胎发育、组织稳态和疾病中扮演重要角色, TGF-β家族配体蛋白通过配体蛋白与细胞表面受体结合启动信号传导, 进而通过调控细胞增殖、表型可塑性、迁移、代谢和多种细胞类型的免疫反应等影响细胞生理过程. TGF-β信号通路对于细胞生物学过程的调控至关重要, 其异常调节与多种疾病的发生发展密切相关. 本综述回顾了TGF-β信号通路的组成和作用机制, 并阐述了其在胚胎发育和疾病中的作用. 不仅探讨了其在干细胞和三胚层发育中的功能, 还总结了其对免疫、纤维化和癌症的影响. 最后, 讨论了如何精准靶向TGF-β信号通路来治疗疾病的新策略.

关键词 TGF-β信号通路, 发育, 免疫, 癌症, 纤维化

TGF-β家族蛋白在发育、组织稳态和疾病发生过程中发挥着重要的调控功能[1~6]. 这些配体通过丝/苏氨酸激酶跨膜受体激活细胞质内的SMAD(drosophila mothers against decapentaplegic protein)转录因子, 激活的SMAD复合物进入细胞核, 与多种转录调控因子结合共同调节下游靶基因的表达, 从而达到对细胞生理过程的调控[7]. TGF-β信号通路除了通过SMAD途径外, 还可通过调控其他信号通路如丝裂原活化蛋白激酶MAPK(mitogen-activated protein kinase)和PI3K-AKT通路来发挥作用[8]. 此外, TGF-β信号通路可以通过相互作用或相互调节与其他信号通路相互作用, 如PI3K-AKT-mTOR通路、Wnt信号通路、Notch信号通路和NF-κB信号通路. 在不同的环境中, 这些相互作用可以放大或调节TGF-β介导的细胞生理功能[9]. TGF-β信号通路的失调与发育障碍、癌症、纤维化、自身免疫炎症反应等多种疾病有关[10~13]. 在过去的几十年中, 大量研究试图揭示TGF-β信号传导在不同细胞和组织类型中的分子机制、生理功能和疾病相关性[1,3,14].

在发育过程中, TGF-β信号通路参与了胚胎发育、器官形成和组织维持等关键过程[2,15~18], 其正常调控对于保证身体各部位的正常发育和功能至关重要. TGF-β信号通路在癌症发生发展过程中的作用备受关注, 因为它具有双重作用, 既可以促进肿瘤的生长和扩散, 也可以抑制肿瘤的发展. 一方面, 在某些情况下, TGF-β信号通路能够抑制肿瘤的生长, 这被称为其抑癌作用. 它可以抑制细胞的增殖, 诱导细胞凋亡, 以及调节肿瘤细胞和周围正常细胞之间的相互作用, 从而抑制肿瘤的生长和扩散. 另一方面, TGF-β信号通路也可以促进肿瘤的发展. 在某些情况下, 癌细胞能够逃避TGF-β信号通路的抑制作用, 并利用其促进肿瘤血管生成、抑制免疫反应、促进细胞迁移和侵袭等特性来推动肿瘤的生长和转移[5,13,19~22]. 除癌症外, TGF-β信号通路在纤维化疾病和自身免疫疾病中也扮演着重要角色[9,10]. 在纤维化过程中, TGF-β信号通路的异常激活导致成纤维细

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胞的增殖和胶原合成增加，最终导致组织瘢痕形成和器官功能受损. 而在自身免疫疾病中, TGF-β信号通路的失调可能导致免疫系统对自身组织的攻击，引发炎症反应和组织损伤[1,4,11,23].

1 TGF-β信号通路

TGF-β信号通路是高度保守的, 其核心成分是细胞外配体、细胞膜表面受体和细胞内SMAD蛋白，首先我们将对这些核心成分进行介绍(表1).

1.1 TGF-β家族配体

TGF-β信号通路的配体根据氨基酸序列相似性和其激活的特异性信号通路，可将其分为TGF-β/Nodal/Activin亚家族和骨形成蛋白(bone morphogenetic protein, BMP)亚家族两大类. 在哺乳动物中，TGF-β/Nodal/Activin亚家族由多种成员组成，包括TGF-β1、TGF-β2、TGF-β3(统称为TGF-β)、Nodal、4种活化素(Activin)、抑制素(Inhibin)、5种生长分化因子(GDF1/3/8/9/15)、及阻断Nodal共受体的LEFTY1和LEFTY2[24~26]. 其中, TGF-β是研究最为透彻的一类, 它们由前体经内切酶作用产生成熟的TGF-β, 后者通常与潜伏相关肽(latency-associated peptide, LAP)形成非共价复合物存在[27,28]. 这种“待活化的TGF-β复合物”需要经过活化过程, 如蛋白酶降解或整合素作用等, 使TGF-β从LAP解离并暴露出与受体结合的区域[28]. 部分TGF-β家族成员还可与潜在TGF-β结合蛋白LTBP或转膜蛋白LRRC32结合[27,29,30]. BMP亚家族包括11种BMP(BMP2-8a/8b/9/10)、4种GDF(GDF5/6/7/10)和抗缪勒氏管素(AMH)[31]. 与TGF-β亚家族不同, 这些配体大多数以活性二聚体形式直接分泌，但也存在一些天然蛋白如NOGGIN、CHORDIN等可与之结合[32~34], 从而阻止其与细胞膜表面受体的结合.

尽管两个亚家族的配体具有一些共同的结构基础, 如二硫键连接的二聚体结构和单体的“半胱氨酸结”等, 但在与膜受体的结合机制和调节方式上存在较大差异[35]. TGF-β/Activin首先与II型受体结合, 然后招募I型受体形成四聚体受体复合物. 而BMP则优先与I型受体结合，再与II型受体相互作用. 不同亚家族成员与受体的结合位点和亲和力也有所区别, 反映了TGF-β信号通路调控的复杂性和多样性. 此外, 许多内源性可溶性蛋白如α2-MACROGLOBULIN、FOLLISTATIN等[36], 能够调节TGF-β家族配体与受体的结合, 在生理和病理过程中发挥重要作用.

1.2 TGF-β家族受体

哺乳动物基因组编码了7种I型受体和5种II型受体, 它们对不同的TGF-β家族配体具有特异的结合偏好[35,37]. 在II型受体中，Activin II型受体(ACVR2)和ACVR2B能与来自不同亚家族的多种配体结合，而骨形成蛋白II型受体(BMPR2)则特异地与BMP亚家族的配体结合, TGF-β II型受体(TGFBR2)和AMH II型受体(AMHR2)仅与TGF-β和AMH相互作用[31].

在TGF-β亚家族中，TGF-β I型受体(TGFBR1, ALK5)与TGF-β、肌肉生成素和GDF11结合, 而Activin I型受体B(ACVR1B, ALK4)和Activin I型受体C(ACVR1C, ALK7)则被其他TGF-β亚家族成员共享. 在BMP亚家族中, 活化素受体样激酶(ACVRL1, ALK1)被BMP9和BMP10共享，Activin I型受体A(ACVR1A, ALK2)、骨形成蛋白I型受体A(BMPR1A, ALK3)和骨形成蛋白I型受体B(BMPR1B, ALK6)则被其他BMP亚家族成员共享[38]. TGF-β家族配体首先结合并募集I型和II型丝/苏氨酸蛋白激酶受体形成复合物，在受体复合物中, II型受体磷酸化并激活I型受体, 后者进一步磷酸化SMAD蛋白(R-SMADs)的C端结构域.

1.3 SMAD蛋白

SMAD蛋白是一类重要的转录因子，在TGF-β和BMP信号通路中发挥关键作用(图1)[39,40]. 在哺乳动物中, 存在8种SMAD蛋白(图2)[8,41]. 这些SMAD蛋白在结构上的N端和C端结构域分别称为MH1和MH2结构域, 之间由一个灵活的连接区分隔开[35,42,43]. N端结构域与DNA结合，而C端结构域含有与I型受体、受体适配蛋白、其他SMADs、核质穿梭因子、DNA结合辅因子、组蛋白乙酰化酶(如p300和CBP)以及染色质重塑蛋白等的相互作用位点. TGF-β亚家族的I型受体主要磷酸化SMAD2和SMAD3，而BMP亚家族的I型受体磷酸化SMAD1、SMAD5和SMAD8，在某些情况下会发生SMAD的交叉激活[44]. 这五种SMAD蛋白被称为“受体调控的SMADs”(receptor-regulated SMADs, R-SMADs). 与许多关键信号介质一样, R-SMADs的表达水平和活性也通过翻译后修饰(尤其是连接区的翻译后修饰)的途径受到严格控制[41,45,46].

R-SMADs的DNA结合活性对于它们作为信号通路的转录因子的作用至关重要. 尽管它们能够与DNA

表 1 TGF-β信号通路成员[1,9]

Table 1 Components of the TGF-β signaling pathway

TGFβ家族	配体	Type Ⅰ型受体	Type Ⅱ型受体	协同受体	SMAD
TGF-β/Nodal亚家族	TGF–β1	TGFBR1	TGFBR2	Beta glycan	SMAD2/3
	TGF–β2	TGFBR1	TGFBR2	Beta glycan	SMAD2/3
	TGF–β3	TGFBR1	TGFBR2	Beta glycan	SMAD2/3
	Activin A	ACVR1B, ACVR1C	ACVR2A, ACVR2B	–	SMAD2/3
	Activin B	ACVR1B, ACVR1C	ACVR2A, ACVR2B	–	SMAD2/3
	Activin C	ACVR1B, ACVR1C	ACVR2A, ACVR2B	–	SMAD2/3
	Activin E	ACVR1B, ACVR1C	ACVR2B	–	SMAD2/3
	Nodal	ACVR1B, ACVR1C	ACVR2A, ACVR2B	cripto/TDGF1, cryptic/CFC1	SMAD2/3
	GDF1	ACVR1B, ACVR1C	ACVR2A, ACVR2B	cripto/TDGF1, cryptic/CFC1	SMAD2/3
	GDF3	ACVR1B, ACVR1C	ACVR2A, ACVR2B	cripto/TDGF1, cryptic/CFC1	SMAD2/3
	GDF8	ACVR1B, ACVR1C	ACVR2A	–	SMAD2/3
	GDF9	ACVR1B	BMPR2	–	SMAD2/3
	GDF11	ACVR1B, TGFBR1	ACVR2A, ACVR2B	–	SMAD2/3
	Inhibin	–	ACVR2A	betaglycan	–
	Lefty1	–	–	cripto/TDGF1, cryptic/CFC1	–
	Lefty2	–	–	cripto/TDGF1, cryptic/CFC1	–
BMP亚家族	BMP2	BMPR1A, BMPR1B	ACVR2A, ACVR2B, BMPR2	RGM	SMAD1/5
	BMP3	–	ACVR2B	–	–
	BMP4	BMPR1A, BMPR1B	ACVR2A, ACVR2B, BMPR2	–	SMAD1/5
	BMP5	ACVR1A, BMPR1A, BMPR1B	ACVR2A, ACVR2B, BMPR2	–	SMAD1/5
	BMP6	ACVR1A, BMPR1A, BMPR1B	ACVR2A, ACVR2B, BMPR2	RGM	SMAD1/5
	BMP7	ACVR1A, BMPR1A, BMPR1B	ACVR2A, ACVR2B, BMPR2	–	SMAD1/5
	BMP8	ACVR1A, BMPR1A, BMPR1B	ACVR2A, ACVR2B, BMPR2	–	SMAD1/5
	BPM8B	BMPR1A, BMPR1B	ACVR2A, BMPR2	–	SMAD1/5
	BMP9	ACVRL1	ACVR2, BMPR2	endoglin/ENG	SMAD1/5
	BMP10	ACVRL1	ACVR2, BMPR2	endoglin/ENG	SMAD1/5
	BMP15	BMPR1B	BMPR2	–	SMAD1/5
	GDF5	BMPR1A, BMPR1B	ACVR2, ACVR2B, BMPR2	–	SMAD1/5
	GDF6	BMPR1A, BMPR1B	ACVR2, ACVR2B, BMPR2	–	SMAD1/5
	GDF7	BMPR1A, BMPR1B	ACVR2, ACVR2B, BMPR2	–	SMAD1/5
	GDF10	BMPR1A, BMPR1B	ACVR2, ACVR2B, BMPR2	–	SMAD1/5
	AMH	ACVR1A, BMPR1A	AMHR2	–	SMAD1/5
	GDF15[a)]		GFRAL		

a) GDF15与TGF-β成员同源性低, 其特异性受体为胶质细胞源性神经营养因子(glial-derived neurotrophic factor, GDNF)样受体α(GDNF receptor alpha-like, GFRAL)

结合, 但这并不足以决定TGF-β靶基因的通路特异性和细胞类型特异性选择. TGF-β信号通路靶基因的选择取决于R-SMADs与特定环境转录因子(TFs)差异性结合的能力, 形成特异性的DNA结合复合物. 通过与细胞特异性的转录调控因子结合, TGF-β活化的R-SMADs和BMP活化的R-SMADs获得对不同靶基因的染色质结合能力, 并产生通路特异性的转录调控[47].

SMAD4不是受体底物, 也不需要用于R-SMAD的核转位, 但它是大多数SMAD介导的转录调控的重要参与者, 也称为Co-SMAD(Common SMAD)[39]. SMAD4所起的具体功能仍有很多未知[48]. SMAD6和SMAD7是抑制性SMADs(inhibitory SMADs, I-

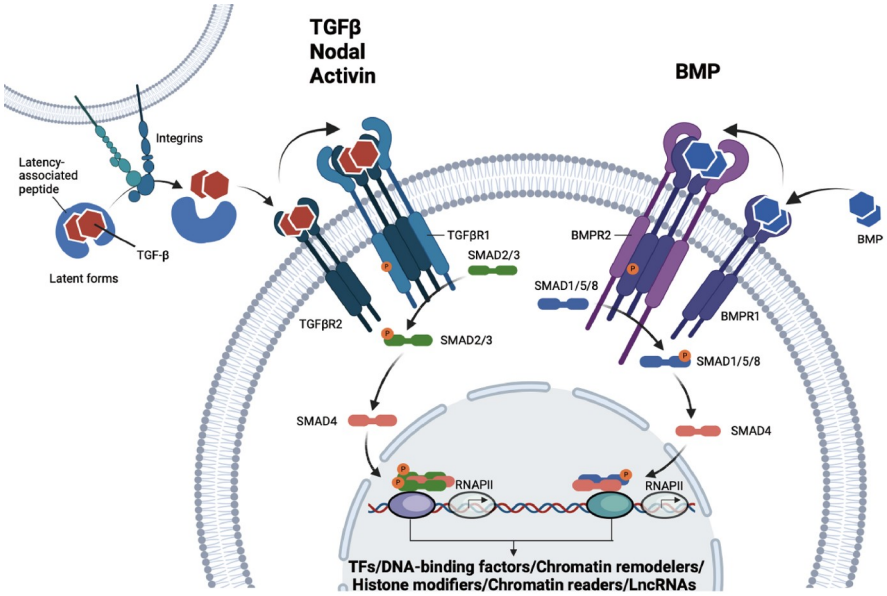

图 1 TGF-β信号通路(图片由BioRender.com生成). TGF-β配体与LAP形成的"待活化的TGF-β复合物"在整合素作用下释放出TGF-β后首先与II型受体结合,然后招募并磷酸化I型受体形成四聚体受体复合物. 受体复合物激活后I型受体磷酸化SMAD2/3, 后者与SMAD4结合形成复合物后进入细胞核, 与多种DNA结合转录因子结合参与基因转录调控. 与TGF-β略有不同, BMP配体大多数以活性二聚体形式直接分泌首先结合I型受体, 再与II型受体结合, 随后磷酸化I型受体形成四聚体受体复合物. 受体复合物磷酸化SMAD1/5/8, 后者同样地与SMAD4结合形成复合物后进入细胞核, 参与基因转录调控

Figure 1 TGF-β signaling pathway(Created with BioRender.com). The "latent TGF-β complex", consisting of TGF-β ligands bound to latency-associated peptide (LAP), becomes activated through integrin-mediated release of TGF-β. Initially, TGF-β binds to the type II receptor, facilitating the recruitment and phosphorylation of the type I receptor, thereby forming a tetrameric receptor complex. Upon activation, the type I receptor phosphorylates SMAD2/3. These phosphorylated SMADs then bind with SMAD4 to form a complex that translocates into the nucleus, where it interacts with various DNA-binding transcription factors to regulate gene transcription. In contrast, BMP ligands are typically secreted as active dimers and directly bind to the type I receptor. This binding prompts the recruitment and phosphorylation of the type II receptor, resulting in the formation of a tetrameric receptor complex. This complex subsequently phosphorylates SMAD1/5/8, which then binds with SMAD4 and translocates into the nucleus, regulating gene transcription in a manner analogous to TGF-β signaling

SMADs), 分别与SMAD4和I型受体相拮抗. TGF-β、BMP、干扰素-γ(IFN-γ)和其他信号诱导SMAD7的表达进而进行负反馈调控[39].

综上所述, 分泌型TGF-β配体、跨膜受体激酶和SMAD效应蛋白, 它们构成了TGF-β信号从细胞表面传递到细胞核的核心信号元件. TGF-β信号通路通过细胞内复杂的传导网络, 对细胞命运和生理过程起着重要的调控作用[49].

2 TGF-β信号通路在胚胎发育过程中的功能

胚胎发育是由各种分子信号通路时空特异调控的过程, 其中TGF-β信号通路发挥着重要作用. 我们将在从三胚层发育、体轴的建立、胚外组织的形成及干细胞维持这些不同的角度探讨TGF-β信号通路的多种功能. 生殖细胞中TGF-β信号通路成分异常(突变)会导致遗传病的产生, 如马方综合征、先天性心脏缺陷等(表2).

2.1 TGF-β信号通路在三胚层发育过程中的调控

在胚胎三胚层形成和器官发育过程中, TGF-β家族成员发挥着关键的调控作用[15,20]. 尤其是Nodal和BMP信号通过精细协调, 参与了三胚层的定位和分化[16]. 背侧组织者区域(Dorsal Organizer Region)是胚胎体节运动开始的部位, 也被称为斯彭曼-曼戈德组织者(Spemann-Mangold Organizer)(绵羊胚胎和斑马鱼)或节区(Node)(小鼠胚胎)[87,88]. 在原肠作用过程中, 上皮细胞向间质转化(Epithelial-Mesenchymal Transition, EMT)是细胞发生迁移运动的关键途径, EMT由SNAIL、ZEB和TWIST转录因子以及平衡这一调控网络的microRNAs驱动[89]. TGF-β信号通路是发育性和纤维性EMT的强效诱导因子, TGF-β信号通路依靠RAS和MAPK通路诱导EMT, 最新的研究表明, RREB1能够连接TGF-β-SMAD和RAS-MAPK通路, 促进特定靶基因的转录表达从而诱导EMT进程[90].

(a)

受体调节型SMAD蛋白 (Receptor-regulated SMADs, R-SMADs)	SMAD1/2/3/5/8
共同介质型SMAD蛋白 (Common SMADs, Co-SMADS)	SMAD4
抑制型SMAD蛋白 (Inhibitory SMADs, I-SMADs)	SMAD6/7

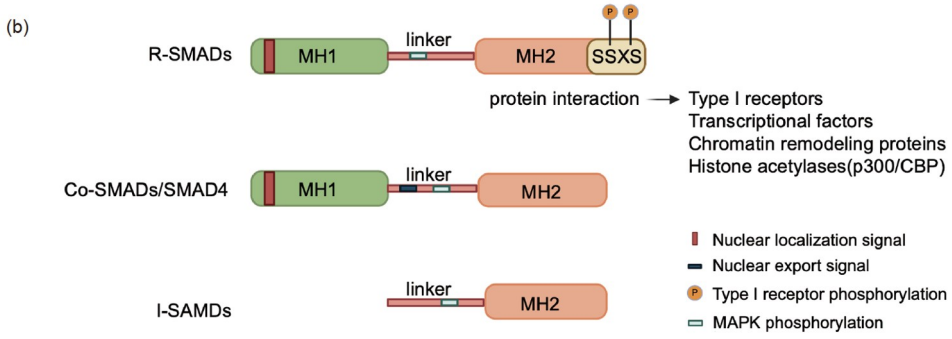

图 2 SMAD效应蛋白(图片由BioRender.com生成). (a) SMAD蛋白分类. (b) R-SMAD由N端的MH1结构域和C端的MH2结构域由linker连接组成. MH1结构域与DNA结合; MH2结构域与蛋白结合, 如I型受体、转录因子和染色质重塑蛋白等. R-SMAD的MH2结构域末端具有SSXS motif, 使其能够被I型受体磷酸化. MH1结构域具有核定位信号, linker区域具有MAPK磷酸化位点. Co-SMAD/SMAD4同样由MH1结构域, MH2结构域和linker组成. 其MH1结构域具有核定位信号, linker区域具有MAPK磷酸化位点和核输出信号. I-SMAD的N端没有典型的MH1结构域, 但仍具有C端MH2结构域和linker, 以及linker上的MAPK磷酸化位点

Figure 2 SMAD TFs. (a) Classification of SMAD proteins. (b) R-SMADs possess an N-terminal MH1 domain and a C-terminal MH2 domain, connected by a linker region. The MH1 domain is responsible for DNA binding, while the MH2 domain facilitates interactions with type I receptors, transcription factors, and chromatin remodeling proteins. At the C-terminus of the MH2 domain, R-SMADs feature an SSXS motif critical for phosphorylation by type I receptors. Additionally, the MH1 domain includes a nuclear localization signal, and the linker region contains sites for MAPK phosphorylation. Co-SMAD/SMAD4 similarly contains an MH1 domain, an MH2 domain, and a linker. The MH1 domain of SMAD4 also has a nuclear localization signal, and the linker region includes MAPK phosphorylation sites as well as nuclear export signals. I-SMADs, in contrast, lack a conventional MH1 domain at the N-terminus but retain a C-terminal MH2 domain and a linker region that includes MAPK phosphorylation sites

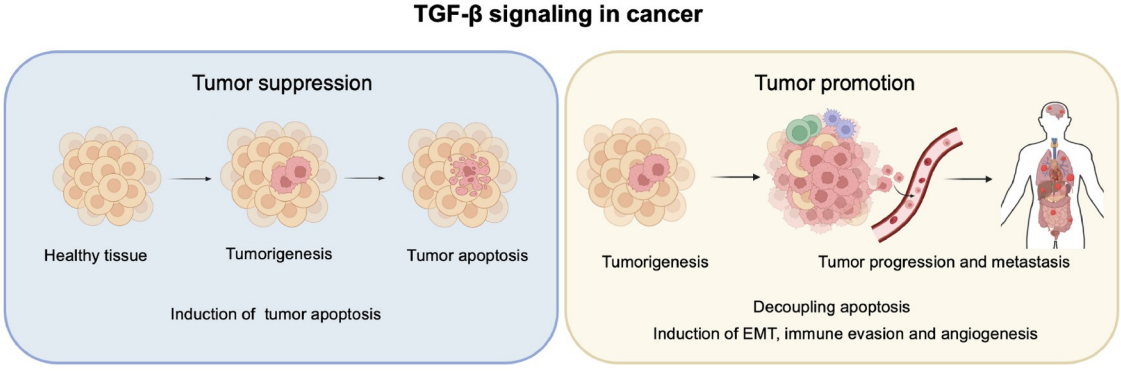

图 3 TGF-β信号通路在癌症中的双重作用(图片由BioRender.com生成). TGF-β信号通路在癌症中的双重作用主要取决于肿瘤的发展阶段. 在癌症发展早期, TGF-β信号通路通过诱导肿瘤细胞凋亡抑制其进一步发展, 从而发挥肿瘤抑制作用. 当癌症进一步发展, 肿瘤细胞TGF-β信号通路与细胞凋亡解耦或失活后, 肿瘤则能够利用自身或微环境中的TGF-β信号通路促进EMT、免疫逃逸、血管生成等方式促进肿瘤的进展和转移

Figure 3 The dual roles of the TGF-β signaling pathway in cancer (Created with BioRender.com). The role of the TGF-β signaling pathway in cancer is significantly influenced by the stage of tumor development. In the early stages, this pathway functions as a tumor suppressor by inducing apoptosis in cancer cells, thereby inhibiting further tumor progression. As cancer advances, the TGF-β signaling pathway within tumor cells may lose its ability to induce apoptosis or become inactivated. At this advanced stage, the tumor can exploit its own TGF-β signaling pathway or that present in the microenvironment to promote progression and metastasis. This occurs through mechanisms such as EMT, immune evasion, and angiogenesis

Nodal是TGF-β家族中一种高度保守的配体, 在早期胚胎发育阶段广泛表达. 研究表明, 在小鼠胚胎早期发育过程中, Nodal信号激活的下游, TRIM33蛋白一方面能够与SMAD2/3-4形成复合物, 另一方面能够识别

表 2　TGF-β信号通路异常与遗传病

Table 2　TGF-β signaling pathway abnormalities and genetic diseases

	突变基因	相关疾病
TGF-β/Nodal亚家族配体	TGFβ1	进行性骨干发育不良[50]
		炎症性肠病和脑病[51]
	TGFβ2	洛伊-迪茨综合征4[52,53]
	TGFβ3	洛伊-迪茨综合征5[54]
		心律失常性心室发育不良[54]
		马方综合征[54]
		主动脉瘤[55]
	Nodal	孤立性心血管畸形[56]
	GDF1	先天性心脏缺陷[57]
	GDF3	眼部和骨骼异常[58]
BMP亚家族配体	BMP2	身材矮小、骨骼和心脏异常[59]
	BMP4	腭裂[60]
		眼部畸形[61]
	BMP6	铁过载[62]
	BMP7	眼、脑、耳、腭和骨骼异常[63]
	BMP9/GDF2	血管异常综合征[64]
	BMP15	高促性腺激素性卵巢衰竭[65]
	GDF5	多发性骨性连接综合征[66]
		A2型短指症[67]
	GDF6	多发性骨性连接综合征[68]
	AMH	持续性苗勒管综合征[69]
Type I型受体	TGFBR1	洛伊-迪茨综合征[70]
	BMPR1B	A2型短指症[71]
	ACVR1A	进行性骨化性纤维发育不良[72]
	ACVRL1	遗传性出血性毛细血管扩张症[73]; 肺动脉高压[74]
Type II型受体	TGFBR2	洛伊-迪茨综合征[70]
	ACVR2B	左右轴发育畸形[75]
	BMPR2	原发性肺动脉高压[76]
	AMHR2	持续性苗勒管综合征[77,78]
SMAD	SMAD1	肺动脉高压[74]
	SMAD2	先天性心脏病[79]
	SMAD3	胸主动脉瘤[80], 洛伊-迪茨综合征3[81], 冠心病[82], 哮喘[83]
	SMAD4	迈尔综合征[84], 肺动脉高压[85], 幼年性息肉病[86]
	SMAD8	肺动脉高压[74]

组蛋白上H3K9me3-H3K18ac双修饰促进中内胚层标志基因的转录，从而决定了中内胚层细胞的命运[91,92]. 在小鼠和人胚胎干细胞中，Nodal信号不仅能够通过p53和WNT3介导活化TCF转录因子促进中内胚层分化相关基因的转录[93]，还能与先锋转录因子FOXH1结合，激活下游中内胚层特异性基因表达[94~96]. 除了Nodal外，Activin作为一种重要的生长因子，在胚胎发育的方方面面发挥着调控作用，参与了从最初的细胞分裂、体节形成到最终器官发育的整个过程[16].

在胚胎早期发育阶段，BMP信号通路能够诱导不同细胞类型分化为特定的器官细胞，例如骨骼、神经等. 在神经系统的形成中, BMP信号通路不仅参与神经管的闭合和神经细胞的分化，还可以影响神经元轴突的生长和突触形成，从而调节神经网络的建立和功能[97,98]. 在骨骼发育中, BMP信号通路在成骨细胞分化中发挥核心调控作用[99]. 但在某些情况下, BMP信号通

路也能诱导破骨细胞分化和骨吸收. 因此, BMP信号通路在调控骨重建过程中发挥双向调节作用. 适度水平的BMP信号通路促进间充质干细胞向成骨细胞分化、成骨细胞功能以及骨形成, 同时抑制破骨细胞的分化和功能, 有利于骨组织的生长和发育, 但过度活化的BMP信号通路则会导致骨质疏松等骨代谢失调、异位骨化等(如斯蒂芬森骨化肌病)[100]. 精确调控BMP信号通路活性水平对于维持正常的骨重建动态平衡至关重要.

总之, TGF-β家族成员通过调控发育相关基因的时空特异性表达, 在三胚层分化的发育阶段发挥着关键调控作用.

2.2 TGF-β信号通路在体节轴发育过程中的调控

在胚胎早期发育中, Nodal在脏器内胚层(anterior visceral endoderm, AVE)中呈现不对称的表达模式, 在后方区域表达较高, 形成一个向前方逐渐降低的浓度梯度[18,101]. 其中, Nodal通过在AVE中诱导其拮抗因子的表达, 形成一个负反馈调控环路, 达到精细调节Nodal浓度梯度的动态平衡[102], 从而建立整个胚胎体节轴的极性格局[103,104]. 总结来说, 较高水平的Nodal/SMAD2/3信号诱导分化形成前体节区和节区等体节前端衍生物, 包括内肠外肺和前体节组织; 中等水平信号则指导心肌细胞和体节旁间充质细胞的形成; 而低水平信号则参与诱导更侧向的中胚层细胞命运, 如侧向间充质细胞. 同时, 一些调节因子如ARKADIA通过调控SMAD2/3复合物的稳定性和转录活性, 精细调节Nodal/SMAD2/3信号强度, 从而指导原肠胚沿体节轴的有序分化, 进而影响肝、胰、肺等内脏和心血管系统等关键结构的形成[2,20].

在胚胎发育中, BMP配体和拮抗剂在背腹轴上呈现明显的不对称表达模式. BMP配体主要在腹侧表达, 而BMP拮抗剂则在背侧和背侧组织者区域高表达[32,33], 而BMP受体和SMAD蛋白则在整个胚胎中广泛表达[105]. 此外, 还有一些调节因子通过影响拮抗剂的结合和降解, 进一步调节BMP信号在体轴形成中的时空分布和活性梯度. 总结来说, 高水平的BMP信号诱导腹侧组织命运, 而BMP信号被阻断则导致背侧组织发育形成脊索、脑和前脊索板等. 因此, BMP信号梯度通过其在体节轴方向上的不对称分布, 调控着下游靶基因的时空表达模式, 进而指导胚胎不同区域细胞分化成不同的组织类型, 是控制胚胎体节轴形成的关键调节因子.

综上所述, TGF-β家族成员Nodal和BMP在胚胎发育中建立的浓度梯度通过精确调控多种发育信号分子的时空活化模式, 引导原肠胚层细胞按照体节轴的位置信息有序分化为不同的胚层细胞类型. 这些信号通路与其他发育调控机制协同作用, 奠定了整个胚胎发育的基本框架, 最终促进了三胚层区域的形成以及各器官系统的发育.

2.3 TGF-β信号通路在胚外组织发育过程中的调控

除了指导胚胎本体的形态建构, TGF-β家族信号分子还参与了胚外组织的形成过程, 这些胚外组织在供给营养和氧气、维持胚胎发育环境等方面发挥着关键作用. 哺乳动物胚胎在子宫内着床时, 形成的囊胚由内上胚层(Inner epiblast, EPI)、滋养外胚层(Trophectoderm, TE)和将形成胎盘的滋养细胞(Trophoblasts, TRs)组成. 在滋养外胚层的发育中, TGF-β信号通路与FGF、Hippo等通路紧密协作调控着细胞命运决定. 在中心区域, TGF-β和FGF维持着干细胞群; 在边缘则介导了分化细胞的迁移. 同时, TGF-β和FGF还调节细胞对分泌素(细胞因子、细胞外基质成分、核酸分子、外泌体等)的反应, 影响滋养细胞分化, 并受到细胞定位的反馈调节. 此外, BMP4在胚泡期的滋养外层细胞中高表达, 诱导滋养外胚层分化[106]. TGF-β/Nodal/Activin信号通路介导了原始内胚层细胞(Primitive Endoderm, PrE)的特异性分化及定位, 促进细胞附着于PrE并形成营养滤泡. Nodal信号通路与FGF信号通路及Wnt信号通路相互作用, 确保了营养滤泡的极性化和结构完整性.

2.4 干细胞的维持和分化

干细胞的特点是具有自我更新和分化成多种细胞类型的能力, TGF-β信号通路对胚胎干细胞(embryonic stem cells, ESCs)的维持和分化起着关键作用[26,107,108]. 在不同干细胞状态下, TGF-β信号通路发挥的功能各不相同. 在小鼠早期胚胎发育中, Nodal是维持并调控内细胞团和滋养层中胚胎干细胞的多能性状态的必需因子, 一旦Nodal功能缺失, 胚胎内细胞团中的干细胞群体失去多能性而过早进入神经分化途径[109]. 随着着床后胚胎的发育, Nodal还参与调节从原始态(naïve)向活化态(formative)的过渡. 成功过渡到活化态后, Nodal则继续维持这一状态的稳定, 确保干细胞具有生殖细胞和体细胞分化的能力.

在体外，Nodal在小鼠胚胎干细胞系的建立和转分化中也扮演重要角色[110]. 原始态的小鼠胚胎干细胞在退出该状态进入活化态时，需要依赖Nodal和FGF等多种信号通路的协同作用[24]. 只有在Nodal存在的情况下，ESCs才能顺利转分化为上胚层干细胞(EpiSC)，并获得体细胞和生殖细胞分化的全能潜能[107]. 在小鼠体细胞重编程为诱导多能干细胞(induced pluripotency stem cells, iPSCs)的过程中，阻断TGF-β信号通路有利于提高重编程效率，因为它能抑制细胞向间质样细胞分化，而BMP信号则促进重编程初始阶段的MET[111]; 而在人体细胞重编程中, 尽管最终TGF-β信号通路的存在有利于iPSCs的获得，但在重编程中期则需要暂时阻断TGF-β信号通路对细胞的间质化诱导作用[112,113].

与之相似, Nodal/Activin/TGF-β信号通路在人源多能性干细胞(human pluripotency stem cells, hPSCs)干性维持中也扮演着关键角色[114]. 首先, 几乎所有hPSCs培养体系中都需要添加Activin A或TGF-β1来维持其多能性[115]. 其次, hPSCs群体内存在着显著的异质性，只有少部分细胞表达较高水平的Nodal通路相关基因，表现出更接近formative的特征. 这一亚群虽然也需要外源Activin/Nodal信号的刺激，但具有更强的自我更新能力, 不易分化. 相比之下, 大部分hPSCs则属于“始发多能态(primed pluripotency)”, 易于分化为神经等特定谱系[116]. 另外，hPSCs中也存在自分泌的Nodal信号环路[24]，自分泌的Nodal在很大程度上也影响着细胞的状态和命运决定.

除了在小鼠和人胚胎干细胞的维持和自我更新中发挥重要作用外, TGF-β信号通路也在成体干细胞中扮演重要角色. 在神经干细胞、造血干细胞和乳腺干细胞群中，TGF-β信号通路促进静止和抑制增殖，从而维持干细胞群体, 这有助于防止干细胞衰竭, 保持其再生能力[24]. 此外, 在肠干细胞中, Wnt和Notch信号通路协同作用维持干细胞的自我更新能力，而BMP信号通路则抑制干细胞的干性特征[117,118]. 在毛囊干细胞中, BMP信号通路不仅阻止干细胞活化进入细胞周期，还限制了其沿毛母细胞方向的分化命运选择，而促进其分化为表皮细胞和角质细胞[119].

3 TGF-β信号通路在疾病中的作用

3.1 TGF-β信号通路在免疫反应中的功能

TGF-β信号通路具有广泛的免疫调节作用, 它作为一种主要的免疫抑制和耐受性诱导因子，对免疫细胞的发育、活化和功能具有广泛的调节作用[4,120]. 首先, TGF-β信号通路对树突状细胞(Dendritic cells, DC)的功能有重要影响. DC在启动和调节T细胞免疫反应中起关键作用. 缺乏TGFBR2的DC会导致多器官炎症和死亡, 这是由于DC无法有效诱导调节性T细胞(T_{reg}), 而过度分泌IFN-γ干扰了Th1和Th17细胞的平衡[121]. 此外, TGF-β信号通路还参与了朗格汉斯细胞(Langerhans cells, 一种皮肤DC)的发育过程[122]. 其次, TGF-β信号通路是调控T细胞分化命运的关键因子, 它促进$CD4^+$ T细胞向T_{reg}细胞的分化，协同FOXP3转录因子启动T_{reg}细胞基因表达程序. 与此同时，TGF-β信号通路通过与RORγt转录因子协同作用促进Th17细胞发育[123~128].

另一方面，TGF-β信号通路抑制Th1和Th2细胞分化，从而维持Th1/Th2/Th17/T_{reg}细胞群的动态平衡. 此外, TGF-β信号通路还直接作用于$CD8^+$ 细胞毒性T淋巴细胞(cytotoxic T lymphocytes, CTL), 抑制其增殖、细胞因子分泌和细胞毒性功能，从而阻断了CTL对肿瘤细胞和病毒感染细胞的免疫杀伤作用[129]. TGF-β信号通路对NK细胞、中性粒细胞、巨噬细胞等其他免疫细胞亦有重要调节作用，它通过抑制NK细胞的多种效应分子表达, 从而阻碍NK细胞的杀伤功能[130,131]. 同时, TGF-β信号通路诱导中性粒细胞和巨噬细胞向具有免疫抑制和促肿瘤特性的亚型转化，抑制其杀伤肿瘤细胞的能力[132,133].

小鼠模型的研究展示了缺乏TGF-β1会导致新生小鼠多器官炎症, 其症状类似自身免疫性疾病. 并且这种表型可被MHC II或β2-微球蛋白基因的缺失挽救. 这说明丧失TGF-β1会引起T细胞的过度激活反应[123,134]. 类似的，在T细胞特异性缺失TGF-β受体或配体也会导致T细胞活化和严重的炎症性疾病[11].

综上所述, TGF-β信号通路在免疫和炎症反应中发挥着关键的作用. 一方面, 它抑制了各类效应细胞的激活和致炎效应, 防止免疫反应失控引发自身免疫病; 另一方面，它促进了T_{reg}细胞的分化，维持机体的免疫耐受. TGF-β信号通路的异常失衡将打破这一微妙的平衡, 进而导致免疫抑制或自身免疫性疾病的发生.

3.2 TGF-β信号通路在纤维化疾病中的功能

纤维化可影响皮肤、肺、肝、肾和心脏等重要器官, 其特点是细胞外基质过度沉积, 导致疤痕和器官功能障碍[10,135,136]. TGF-β信号通路主要是通过作用于成

纤维细胞和上皮细胞而发挥纤维化效应[10]. TGF-β是一种强大的成纤维细胞激活剂，能促进成纤维细胞产生α-平滑肌肌动蛋白、多种细胞外基质成分以及组装和交联胶原蛋白所需的酶和分子伴侣. 活化的成纤维细胞还能分泌多种细胞因子，与上皮细胞、免疫细胞和内皮细胞进行旁分泌调控. TGF-β信号通路还能通过诱导整合素的表达，从而增强细胞与细胞外基质的相互作用，形成正反馈调控环路. 除了作用于成纤维细胞外, TGF-β信号通路也能通过诱导上皮细胞表达整合素αvβ6、抑制上皮细胞增殖以及诱导上皮细胞衰老和死亡等途径促进纤维化，特别是上皮细胞衰老可能是导致纤维化(尤其是肺部纤维化)的重要驱动力[135]. 此外, TGF-β信号通路可以通过诱导内皮生长因子VEGF等因子的表达, 促进新生血管生成, 为纤维化组织提供营养支持[137]. TGF-β信号通路的过度激活会导致伤口愈合反应失调，造成产生基质的肌成纤维细胞和过多的细胞外基质(ECM)聚集, 从而使纤维化长期存在[138,139]. 总之, 过度或持续的TGF-β信号传导也会引发病理性纤维化, 最终导致器官功能衰竭.

在纤维化疾病中，转分化是一个重要的生物学过程，涉及细胞功能的转变和活化. TGF-β信号通路在纤维化疾病中的转分化过程中起着核心作用，通过调节成纤维细胞的增殖、存活、代谢和ECM合成，推动了纤维化的发展[140]. 在受损的肾脏中，分化不良的肾小管上皮细胞会分泌多种关键分子，激活周围血管细胞, 并促进其向肌成纤维细胞的转分化. 这些血管细胞在肾纤维化过程中过度增殖, 并产生细胞外基质, 从而加剧肾脏损伤[141]. 此外, TGFβ信号通路还能够诱导血管细胞中的基因发生超甲基化[142,143], 从而进一步促进纤维化过程. 在心肌梗死等心脏疾病后, 心脏成纤维细胞通过TGF-β信号通路的激活而转分化为肌成纤维细胞[138,144]. 这一过程涉及到多种细胞类型和信号分子的相互作用, 包括心脏成纤维细胞、免疫细胞, 以及细胞表面受体. TGF-β作为一种多功能细胞因子，能够促进成纤维细胞的增殖、迁移，并诱导它们表达肌成纤维细胞特异性蛋白，如α-平滑肌肌动蛋白(αSMA). 此外, TGF-β还能激活心脏成纤维细胞中的Yap/Taz，这些转录共激活因子进一步促进了心肌梗死后心脏纤维化的发展[144]. 类似地，肝星状细胞在静息状态下负责代谢和储存视黄醇, 维持ECM的平衡. 但在肝纤维化中, 受到刺激的肝星状细胞会转分化为肌成纤维细胞，失去视黄醇，上调αSMA，并开始产生胶原蛋白，从而导致纤维化的形成[145].

3.3 TGF-β信号通路在遗传性疾病中的功能

TGF-β信号通路在多种遗传性疾病中扮演着关键角色，这些疾病包括但不限于遗传性出血性毛细血管扩张症[73]、肺动脉高压[74,76]、先天性心脏病[57,79]、马方综合征[54]以及洛伊-迪茨综合征[52~54,70]等. 在遗传性疾病中，TGF-β信号通路的失调，如异常激活或抑制, 可能导致从骨骼畸形、心血管问题到器官纤维化等一系列病理变化(表2).

近年来, 多种家族性血管疾病的研究揭示了TGF-β家族受体的重要性. 这些疾病的主要临床表现包括黏膜皮肤组织中的小血管病变出血和动静脉畸形. TGF-β信号通路还与肺动脉高压有关，这是一种以肺动脉平滑肌层肥厚和毛细血管前小动脉内膜增厚为特征的严重肺部疾病. 家族性肺动脉高压与BMPR2基因的功能性缺失突变有关，该基因编码的受体在肺动脉平滑肌细胞和内皮细胞中水平下降, 导致SMAD1激活减少和/或p38丝裂原激活蛋白激酶(MAPK)激活增加，可能导致血管平滑肌细胞的过度增殖[76].

TGF-β信号通路的增强与主动脉瘤的发展有关[55], 这是马方综合征和洛伊-迪茨综合征等临床疾病的重要特征. 这些疾病中, 由于TGF-β信号通路的过度活化, 导致主动脉根部的易损性增加，增加了主动脉夹层、破裂和猝死的风险. 此外，在妊娠期高血压疾病，如先兆子痫中, 也观察到TGF-β信号通路的变化[146]. 先兆子痫患者体内循环的可溶性VEGF受体-1(sFLT1)水平升高，可能通过减少VEGF配体与内皮细胞上VEGF受体的接触来发挥作用. 同样，可溶性endoglin的水平升高也可能与sFLT1协同作用, 通过结合循环TGF-β, 从而抑制TGFBR2和ALK5依赖的信号传导，导致一氧化氮合酶-3(NOS3，eNOS)的激活水平降低，血管舒张反应减弱, 从而导致先兆子痫.

3.4 TGF-β信号通路在癌症中的双重作用

TGF-β信号通路在癌症中表现出双重作用, 既能抑制肿瘤也能促进肿瘤进展，主要取决于肿瘤的类型和发展阶段. 在癌症早期，TGF-β信号通路通过诱导细胞凋亡来抑制前癌细胞的恶性转化，发挥肿瘤抑制作用. 但一旦癌细胞通过解耦该通路与凋亡的关联而逃脱凋亡命运，TGF-β信号通路反而会通过促进EMT、免疫逃逸、血管生成等方式促进肿瘤进展和转移[13,20,21,120].

在胰腺癌中, TGF-β信号通路诱导凋亡的分子机制主要是通过其对细胞命运决定性转录因子(如SOX4和KLF5)的调控来实现的. 在具有癌基因突变(如KRAS)的癌前病变上皮祖细胞中, TGF-β信号通路与RAS/MAPK途径交互作用, 导致SOX4和KLF5的功能失调, 从而引发"致命性EMT"进程, 最终诱导细胞凋亡[147]. 这种肿瘤抑制作用在胰腺、肠道、皮肤等组织的小鼠模型中均已得到验证.

然而, 在许多实体瘤中常见的是TGF-β信号通路失活突变, 如结直肠癌中的TGFBR2突变、胰腺癌中的SMAD4缺失等. 这些突变破坏了TGF-β信号通路导致细胞凋亡的能力, 使得肿瘤克服了TGF-β信号通路的抑制作用. 即使在保留完整TGF-β信号通路的肿瘤中, 癌细胞也能通过其他机制如激活PI3K/AKT信号来解耦EMT与凋亡, 继而利用TGF-β信号通路促进EMT、干细胞特征维持、骨转移等过程. 值得注意的是, 即便肿瘤中的TGF-β信号通路被完全失活, 肿瘤细胞仍然可以利用肿瘤微环境中的TGF-β来支持肿瘤进展, 如诱导癌相关成纤维细胞分泌促进转移的细胞因子[19,148].

弥漫性胶质细胞瘤(DIPG)是一种罕见且无法根治的儿童脑癌, 患者存活期不足一年. 约80%的DIPG病例携带H3K27M突变, 被认为是DIPG发病的驱动因素[149,150]. 约20%的DIPG患者同时携带ACVR1基因突变, ACVR1编码BMP I型受体[22], 在这一亚型中, ACVR1突变能够独立于配体激活BMP信号通路. 研究表明, 独立于配体激活的BMP信号通路在这一亚型中能够促进癌症的发生发展[148]. 大约60% ACVR1野生型且携带H3K27M的DIPG病例, BMP则可通过SMAD依赖的方式促进DIPG肿瘤细胞的分化从而抑制肿瘤[148]. 总的来说, BMP信号通路在DIPG的不同亚群中可能发挥不同的作用, 这些发现为DIPG的个体化精准治疗提供了新的线索.

总之, 在癌症发生发展的不同阶段, TGF-β信号通路通过其复杂的调控网络发挥着截然不同的功能. 阐明这一转折点的分子机制对于理解癌症发生发展至关重要, 也为开发有效干预TGF-β信号通路功能的新策略提供了线索[9,11,23].

4 展望

本综述总结了TGF-β信号通路在多细胞生物整个生命周期中作为组织稳态的中央调控因子的功能. 近年来, 随着对TGF-β信号通路在生理和病理过程中作用机制的深入研究, 人们对其复杂的双向调节作用有了更全面的认识. TGF-β信号通路在不同的细胞环境中参与多种调节, 产生了细胞环境依赖的功能输出. 一方面, TGF-β信号通路在发育、组织稳态, 免疫调节、伤口修复等生理过程中发挥关键作用. 另一方面, TGF-β信号通路的中心性也使其容易形成异常的通路调控, 导致疾病的逐渐发生发展[1,5,9]. 因此, 持续关注TGF-β信号通路系统运作逻辑的解析将有助于发现更多有效的策略, 以精确地针对其病理作用, 同时保留其关键功能.

针对TGF-β信号通路的治疗策略涉及其生物合成、激活和信号传导的各个层面. 例如, Trabedersen作为一种反义寡核苷酸, 能够特异性抑制TGF-β2的生物合成, 并在胶质瘤患者的临床试验中显示出长期生存率的提高[151]. 通过设计肿瘤细胞疫苗以降低TGF-β表达, 如Lucanix疫苗, 在非小细胞肺癌(NSCLC)患者中观察到生存优势[152]. 针对TGF-β激活的策略中, SRK-181抗体能够选择性结合潜伏态TGF-β1, 抑制其激活, 并在小鼠模型中显示出显著的抗肿瘤效果[153]. 此外, Fresolimumab作为一种中和所有3种TGF-β亚型的单克隆抗体, 在多项临床研究中显示出安全性和抗肿瘤活性的初步证据[154]. 除了直接靶向TGF-β信号通路的组分外, 还有治疗策略能够通过更精确地针对特定细胞或下游介质来治疗TGF-β信号通路相关的疾病[9,155].

TGF-β信号通路的双向作用为针对其进行治疗干预带来了极大挑战. 全身广谱抑制可能产生严重毒副作用, 而小分子抑制剂的靶向特异性、生物制剂的体内滞留中和等均是亟需解决的难题. 因此, 最新的研究重点逐渐转向提高干预的时空精准性和靶向特异性. 一种新兴策略是结合最新的细胞和合成生物学技术, 将TGF-β信号通路的抑制元件整合进CAR-T等细胞治疗产品, 实现局部定点可控调节肿瘤微环境的免疫功能[156]. 另一种思路则是通过精准作用于TGF-β信号通路下游的特异效应分子, 来规避对通路的全面抑制[157~159]. 虽然针对TGF-β信号通路的治疗手段已取得重大进展, 但由于该通路的复杂性和多面性, 实现精准可控的干预仍是一大挑战. 未来需要更深入理解TGF-β信号网络的调控机制, 全面把握其在不同细胞状态和疾病状态下的差异化作用模式, 结合新技术新策略(如靶向给药等)来降低毒副作用、提高特异性, 才能真正实现精准给药, 充分发挥TGF-β这一关键通路的治疗潜能.

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Summary for “TGF-β信号通路在发育和疾病中的调控”

TGF-β signaling pathway in the regulations of development and disease

Hongyao Sun[1], Sixuan Wei[2] & Qiaoran Xi[1]

[1] *School of Life Sciences, Tsinghua University, MOE Key Laboratory of Protein Sciences, State Key Laboratory of Molecular Oncology, Beijing 100084, China;*
[2] *Tsinghua-Peking Center for Life Sciences, School of Life Sciences, Tsinghua University, Beijing 100084, China*
* Corresponding author, E-mail: xiqiaoran@mail.tsinghua.edu.cn

The Transforming Growth Factor-β (TGF-β) signaling pathway plays a crucial role in regulating various essential biological processes, including embryonic development, tissue homeostasis, immune response modulation, and wound healing in multicellular organisms. TGF-β family ligands initiate signaling cascades by binding to specific cell surface receptors, regulating diverse cellular activities such as proliferation, phenotypic plasticity, migration, metabolism, and immune responses across various cell types. Upon ligand binding, TGF-β receptors undergo phosphorylation, activating intracellular SMAD proteins that translocate to the nucleus to influence gene expression. In addition to the canonical SMAD pathway, non-SMAD pathways are also activated, contributing to the wide range of cellular responses elicited by TGF-β signaling. This pathway’s versatility and extensive impact are evident across multiple physiological and pathological contexts. Dysregulation of the TGF-β signaling pathway is closely associated with the development and progression of numerous diseases. For instance, aberrant TGF-β signaling is a hallmark of fibrosis, characterized by excessive connective tissue deposition, leading to tissue scarring and impaired organ function. In cancer, TGF-β exhibits a dual role: it acts as a tumor suppressor in the early stages by inhibiting cell proliferation, but in advanced stages, it promotes tumor progression by facilitating epithelial-mesenchymal transition (EMT), invasion, and metastasis, as well as modulating the tumor microenvironment to evade immune surveillance. This review provides a comprehensive examination of the components and mechanisms underlying the TGF-β signaling pathway. It emphasizes the pathway’s critical role in embryonic development, including its involvement in germ layer formation, organogenesis, and body patterning. Additionally, the review highlights the significance of TGF-β signaling in stem cell biology, where it regulates stem cell maintenance, differentiation, and interactions within the stem cell niche. The review further delves into the implications of TGF-β signaling in various diseases, particularly its impact on immune regulation, fibrosis, and cancer progression. The ability of TGF-β to modulate immune responses is especially pertinent in chronic inflammatory conditions and cancer, where it can suppress anti-tumor immunity and foster an immunosuppressive environment conducive to tumor growth. Finally, the review explores emerging therapeutic strategies targeting the TGF-β signaling pathway for disease treatment. These strategies include the development of small molecule inhibitors, neutralizing antibodies, and receptor kinase inhibitors that aim to modulate the pathway’s activity. By targeting specific elements of the TGF-β signaling cascade, these therapeutic approaches hold significant promise for treating diseases associated with TGF-β dysregulation, offering potential for improved clinical outcomes. In sum, this review provides a comprehensive analysis of the TGF-β signaling pathway, elucidating its critical roles in both physiological and pathological contexts. It underscores the necessity for ongoing research to develop innovative therapeutic strategies, with the goal of leveraging the pathway’s potential for clinical applications.

TGF-β signaling pathway, embryonic development, immunity, cancer, fibrosis

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