紧密连接的构成、装配及其调控研究进展

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摘要 紧密连接(TJ)是存在于所有上皮或内皮细胞连接最顶端的大分子复合物, 主要由胞浆蛋白和跨膜蛋白构成, 是物质旁细胞转运途径和细胞极性维持的结构和功能基础. 此外, TJ双向参与细胞信号的调控, 不仅接收来自细胞内部的信号, 调控TJ蛋白的装配和成熟; 还可传递外来信号到细胞内部调控细胞的增殖、迁移、存活和分化. 本文重点介绍了细胞TJ的分子构成、装配和功能调控方面的最新进展, 并综述了TJ在肿瘤发生和发展、丙肝病毒感染和遗传性耳聋中的功能, 以期防治与TJ改变相关的上皮疾病提供理论指导.

关键词 紧密连接, 分子构成, 装配, 功能调控

紧密连接(tight junction, TJ)是由多种蛋白及分子构成的具有多种功能的大分子复合物, 广泛存在于所有上皮或内皮细胞间连接的最顶端. 在体内, 水、离子和氨基酸、葡萄糖等可溶性分子的转运可通过跨细胞和旁细胞两种途径实现. TJ使上皮细胞形成高度极性的屏障, 该“屏障”功能可对物质的大小和电荷进行选择, 进而调控旁细胞途径的物质转运; TJ还可通过阻止细胞膜中的脂质和蛋白等的自由流动, 将上皮细胞膜划分为顶膜和基底侧膜两部分, 完成其“栅栏”功能. 近年来, 关于TJ的作用及调控机制的研究日益增多, 本文将重点介绍TJ的构成、装配、相关信号调控机制及在肿瘤、丙肝等疾病研究中的最新研究进展.

1 TJ的构成

根据亚细胞定位可将TJ蛋白分为跨膜蛋白和胞浆

蛋白. 跨膜蛋白通过胞外环相互结合形成“拉链”状的“嵴线”结构, 封闭细胞旁间隙; 胞浆蛋白则作为桥梁连接跨膜蛋白和细胞骨架蛋白, 形成一个完整的网状结构(图1).

1.1 跨膜蛋白

(1) Occludin. Occludin是最早被发现的跨膜蛋白^[1]. 分子量约为65 kD, 表达于两个细胞的接头处, 具有4次疏水跨膜结构域, 其N-端和C-端都在胞质内, 有一个胞内环, 两个胞外环. Occludin蛋白的胞外环有很多保守的甘氨酸和酪氨酸, N-端和C-端结构域有很多丝氨酸和苏氨酸残基. Occludin蛋白的表达与各种组织和器官的屏障相关^[2]. 有证据表明, Occludin蛋白并不是TJ完整性的必要的组分, 像胚胎干细胞这样并不表达Occludin的一些细胞也能够形成TJ^[3]. Saitou等

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图1 紧密连接的构成及装配模式图

人^[4]的实验已经能够敲除小鼠(*Mus musculus*)的Occludin, 尽管这些小鼠在很多组织形态上反常, 但是它们的肠上皮的电生理学表现正常。

(2) Claudin家族. 迄今已发现27个Claudin家族成员, 分子量均约为20~27 kD. 基于序列相似度的分析, 可以把Claudin家族成员分为典型和非典型两类, 典型的Claudin蛋白研究的比较多, 表现出最大的同源性, 包括Claudin1-10, Claudin-14, Claudin-15, Claudin-17和Claudin-19; 非典型的Claudin蛋白包括Claudin11-13, Claudin-16, Claudin-18和Claudin20-24^[5,6]. Claudin蛋白家族均为4次跨膜, 其N-端和C-端都在胞质内, 含一个胞内环和两个胞外环^[7,8]. Claudin蛋白第一个大的胞外环具有带电的氨基酸, 能够调控阳离子和阴离子, 具有旁细胞离子选择性, 胞外环中还有两个高度保守的半胱氨酸残基, 推测通过形成二硫键增加蛋白的稳定性; 第二个短的胞外环通过保守的芳香残基间的相互作用参与Claudin二聚体的形成. C-端尾巴在所有的Claudin中表现出最大的异质性(序列和长短), 除了Claudin-12外, 所有的Claudin家族成员都在C-端含有PDZ结构模

体, 这一结构域允许Claudin蛋白和包含有PDZ结构域的接头蛋白相互作用. 此外, 位于Claudin蛋白PDZ结构上游的C-端序列对Claudin蛋白正确定位到TJ复合物起到不可或缺的作用, 这些区域是丝氨酸/丝氨酸/酪氨酸磷酸化^[9,10]、SUMO化^[11]和棕榈酰化位点^[12]. Claudins家族蛋白的分布呈组织特异性, 例如, 肾脏Claudin-2蛋白主要分布于肾小管近端, 在Claudin-2蛋白形成的TJ旁通道的帮助下完成大部分的Na⁺, K⁺和水的重吸收^[13,14].

(3) JAM家族. JAM属于免疫球蛋白超家族成员, 包括JAM A/B/C/4/L 5个成员, 分子量约为40 kD, 均为单次跨膜糖蛋白^[15]. 基于序列相似性, JAM分为两个亚类, JAM A/B/C属第一亚类, 在其C端有II类包含有PDZ结构域的模体, 直接与ZO-1和Par-3相互作用; JAM 4/L属第二亚类, 在其C端有I类包含有PDZ结构域的模体^[16]. JAM和Occludin, ZO-1等TJ蛋白形成复合体参与TJ的形成, 广泛表达于淋巴组织、脑内皮细胞及多种上皮细胞中, 在内皮细胞的迁移、血管功能的维持及细胞通透性的调控等过程中发挥作用^[17].

(4) *Tricellulin*. *Tricellulin*只表达于三细胞连接处, 分子量约为63.6 kD, 为4次跨膜蛋白, N-端和C-端位于胞浆内, 其中C-端130个氨基酸残基与*Occludin*序列一致, 推测*Tricellulin*也可受磷酸化的调节. 在功能上, *Tricellulin*与跨膜蛋白*Occludin*能形成互补作用, 在加强三细胞TJ、调控大分子物质经旁细胞途径的转运及维持TJ网状结构中发挥重要的作用^[18,19]. 2017年最新报道, 合成肽*Trictide* (衍生于*tricellulin*蛋白第二个细胞外环)可使*Tricellulin*从三细胞连接转位到两细胞连接, 并使*Claudin-1*和*Occludin*由胞膜向胞浆重分布, 最终增加离子、小分子和大分子的渗透性^[20].

(5) *Angulin*. *Angulin*家族(*Angulin 1~3*)也表达于三细胞接头处, 是具有免疫球蛋白样结构域的单次跨膜蛋白. *Angulin*募集*Tricellulin*于三细胞接触处, 这对于TJ的形成及屏障功能的发挥是不可或缺的^[21]. 2017年, 最新报道的*Angubindin-1*蛋白可通过结合*Angulin-1*使*Angulin-1*和*Tricellulin*从三细胞连接处解离, 增强细胞对大分子物质的通透性^[22].

1.2 胞浆蛋白

(1) ZO家族分子. ZO蛋白属于膜相关鸟氨酸激酶(membrane-associated guanylate kinase, MAGUK)家族, 是构成TJ网状结构的“桥梁”, 参与维持和调节极性细胞的屏障功能. ZO家族包含ZO-1~3, 分子量分别为220, 160和130 kD, ZO-1是TJ中第一个被发现的胞浆蛋白. ZO家族分子以N端的3个PDZ结构域(PDZ-1~3)、中部的SH3结构域和GUK结构域, 以及脯氨酸富集区为特征. 其中, PDZ1可与跨膜蛋白*Claudins*的C端结合, 对于TJ的组装具有重要作用; PDZ2可介导ZO蛋白之间的相互作用, 形成同源或异源二聚体, 对TJ结构和功能的调控具有重要作用; PDZ3可与跨膜蛋白JAM结合; SH3结构域是一含有约60个氨基酸残基的小蛋白结构域, 与病毒接头蛋白c-Crk、磷酸酶和很多胞质酪氨酸激酶非催化部分有同源性, 促进JAM与PDZ-3结构域相互结合, 能够结合脯氨酸丰富的配体, 介导大的多蛋白复合物装配^[23,24]; GUK结构域与鸟苷酸激酶具有序列相似性, 介导蛋白质互作^[25]; 脯氨酸富集区定位在ZO-1和ZO-2的C端, ZO-3的PDZ2与PDZ3之间, 主要介导ZO蛋白与细胞骨架蛋白F-actin及骨架相关蛋白Cortactin、 α -catenin、蛋白4.1R和Cingulin等的相互作用, 因此又被称为细胞骨架结合

区. 此外, 在ZO蛋白的保守序列间还存在一些高度可变的结构域, 命名为U1~U6, ZO-1的SH3-U5-GUK-U6功能模块对于TJ的装配和定位很重要, SH3和GUK结构域通过分子互作决定U5和U6模体的位置, 调节ZO-1与*Occludin*及其他蛋白的结合能力^[26].

(2) *Cingulin*. *Cingulin*的分子量为140 kD, 其N-端与ZO-1和细胞骨架蛋白(主要是F-actin)相结合, 在TJ中发挥着连接细胞骨架与胞浆蛋白的作用. 其结构为一细长的螺旋-螺旋二聚体, 与肌球蛋白尾巴相似, 包含头结构域和尾巴结构域. 序列分析表明, 它与肌球蛋白有部分同源性, 表明*Cingulin*和肌动蛋白间可能会发生相互作用, 在TJ渗透压调节中发挥重要作用. 有研究表明, *Cingulin*基因敲除小鼠的上皮组织具有正常的TJ结构, 但*Claudin-2*, -6和-7的基因表达水平增加, 提示*Cingulin*的缺失对TJ复合物的形成并没有影响. 此外, *Cingulin*可在腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)的作用下发生磷酸化, 进而增强TJ和细胞骨架微管系统的结合性^[27].

2 TJ的装配

以往研究表明, ZO-1是参与TJ装配的关键调节蛋白, 它将*Occludin*, *Claudins*和JAMs等跨膜TJ蛋白的胞内区与骨架蛋白等多种胞浆蛋白相连, 调节细胞内外信号的传递, 改变肌动蛋白的收缩性, 调节TJ的装配. 随着对TJ装配的深入研究, 近来发现黏附连接、上皮极性复合物及AMPK介导的信号通路在TJ的装配调节中起关键作用(图1).

2.1 黏附连接起始TJ装配

有研究表明, 细胞黏附连接是TJ装配的起始信号, 在钙离子依赖的E-钙黏素(E-cadherin)介导的细胞黏附建立之后, 与catenin和afadin相互作用的ZO蛋白游离并转位到顶端^[28,29], 继而招募跨膜蛋白*Claudin*, *Occludin*和JAM到黏附连接顶端, 但这些蛋白如何招募到该处的机理还不是很清楚. 由于ZO蛋白和这些跨膜蛋白建立了强相互作用, ZO蛋白完全转位到最顶端参与成熟TJ的装配^[30].

2.2 嵴线的形成

TJ装配起始后, 主要的跨膜蛋白*Occludin*和*Clau-*

dins可通过其胞外环以“拉链”状结合, 形成连续的“焊接线”围绕在细胞的四周, 即嵴线, 由于这些TJ蛋白颗粒的直径只有几个纳米, 因此相邻细胞之间的质膜结合紧密, 封闭了细胞间隙, 在维持TJ的屏障功能和通透性上起着关键作用. 细胞对小分子的通透性与嵴线的数量密切相关, 有些TJ甚至连水分子都不能透过^[31]. 胞浆蛋白ZOs可将Occludin, Claudins和JAMs等跨膜蛋白的胞内区与骨架蛋白等多种胞浆蛋白相连, 并将不同的信号传递到跨膜蛋白Claudins, Occludin, 对TJ结构的“开启”与“闭合”进行调控, 例如, 在颌下腺移植的家兔(*Oryctolagus cuniculus* f. *domesticus*)泪溢模型研究中发现, 降低ZO-1与Occludin的相互作用可导致腺体紧密连接结构“开启”, 家兔泪溢增加^[32].

2.3 上皮极性复合物调控TJ装配

TJ对于细胞极性的维持非常重要, 有三类进化保守的蛋白复合物参与上皮细胞极性、黏附和TJ的建立, 分别是Crumbs3-Pals-PatJ, Par3-Par6-aPKC和Scribble-Dlg-Lgl复合物. 其中, (i) Crumbs3-Pals-PatJ复合物中的Crumbs3主要在骨骼肌和上皮细胞表达, Crumbs3的PDZ和FERM结合域对TJ的形成尤其重要^[33]; 脚架蛋白Pals与Crumbs3的相互作用对于连接装配和顶端结构域的建立很关键; PatJ与ZO-3, Claudin-1和JAM相互作用, 可促进ZO-1从黏附连接分离出来^[34]. (ii) Par3-Par6-aPKC复合物中, 在未形成TJ时, aPKC和Par6定位于胞质, 并与Lgl蛋白相互作用, 阻止了aPKC-Par6和Par3形成三元复合物^[35]. 装配开始后, Nectin可促进Par3定位于黏附连接处, 并使Cdc42活化并转位到顶膜, 活化的Cdc42可进一步活化aPKC, aPKC则磷酸化Lgl, 促进Lgl从aPKC和Par6复合中释放并转位到基底膜^[36-38]. (iii) Scribble-Dlg-Lgl复合物建立起基底结构域, 阻止顶端结构域中的蛋白分布到基底结构域. 该复合物的缺失可导致顶端蛋白错误分布, 但是基底蛋白分布不受影响^[34]. 这三类极性复合物相互作用, Crumbs-Pals-PatJ和Scribble-Dlg-Lgl复合物调控Par3-Par6-Apkc的定位, 一起协调促进TJ的装配, 建立起顶膜和基底膜的界限, 维持正常细胞连接复合物和组织稳态^[39].

2.4 AMPK信号调控TJ装配

在果蝇(*Drosophila melanogaster*)、新杆状线虫及

哺乳动物细胞中均发现, AMPK在TJ的装配和细胞极性的建立过程中发挥着关键的作用, 其活性的丧失导致细胞极性发生改变^[40,41]. Wu^[42]使用MDCK细胞作为细胞模型, 采用钙转换实验和药物处理相结合的方法, 发现激活AMPK可帮助aPKC ζ 和Par3定位到TJ起始装配处, 促进Cdc42结合GTP而活化, 进而磷酸化Afadin S1102位点并加强ZO-1和Afadin间的互作, 促进TJ的装配. 此外, Zhang等人^[43]研究表明, 激活AMPK和抑制GSK-3 β 以钙离子非依赖方式诱导TJ在质膜处的定位. Aznar等人^[44]研究表明, AMPK可通过磷酸化极性脚架蛋白Gridin蛋白的S225从而稳定正常上皮TJ功能. Sun等人^[45]发现, AMPK通过促进CDX2的表达, 加强肠屏障功能和上皮分化.

3 TJ的调控

TJ双向参与细胞信号的调控, 不仅接收来自细胞内部的信号(如生长因子、细胞因子和激素等), 调控TJ蛋白的装配和成熟; 还可传递外来信号(如药物、细菌、病毒等)到细胞内部调控细胞的增殖、生长和分化. 这些内源性或外源性的刺激因素可通过改变TJ蛋白的表达水平、细胞学分布、磷酸化状态、泛素化状态, 以及TJ蛋白间相互作用等改变旁细胞途径通透性, 调节TJ的结构和功能.

3.1 改变TJ蛋白的表达水平和分布情况

TJ蛋白表达的改变, 内吞、内化及膜转位等细胞学定位的改变对于TJ功能的发挥至关重要. 研究表明, IL-22可通过JAK-STAT途径上调Claudin-2的表达, 导致跨上皮电阻值下降, 肠上皮渗透性增加^[46]. 另外, 在用益生菌处理尿毒症组肠上皮细胞实验中, 益生菌抑制了TLR 4-NF- κ B信号通路, 使TJ相关蛋白Occludin, Claudin-1, JAM-1表达水平上调, 且其表达分布由肠黏膜表面向隐窝部位移位^[47]. 肠出血性大肠杆菌(*Enterohemorrhagic Escherichia coli*)通过效应蛋白使Tricellulin的表达下调, 破坏上皮的屏障功能^[48]. 在骨肉瘤细胞发生转移时, Claudin-1可从细胞膜转位入核, 激活PKC可通过上调Claudin-1的表达进一步促进骨肉瘤细胞细胞的迁移能力^[49].

3.2 引起细胞骨架蛋白F-actin的重排

TJ蛋白可与细胞骨架F-actin相连形成TJ复合体,

维持旁细胞途径的功能. 在乳兔颌下腺细胞中, 通过辣椒素处理提高ERK1/2和MLC2磷酸化水平, 进而ERK1/2磷酸化介导辣椒素受体(transient receptor potential cation channel subfamily V member 1, TRPV1)对TJ蛋白表达进行调控, MLC2磷酸化使ZO-1, Occludin及TJ周围骨架蛋白F-actin发生重排^[50].

3.3 改变TJ蛋白磷酸化水平

TJ蛋白的磷酸化和去磷酸化水平在TJ的分布和功能调控中非常关键. 在TJ的细胞中, Occludin在Tyr-残基上的磷酸化水平较低, 在Ser-和Thr-残基上的磷酸化水平则较高; 相反, 在未形成或遭到破坏的TJ细胞中, Occludin的Ser-和Thr-残基发生去磷酸化, 而Tyr-残基的磷酸化水平增加, 推测Occludin通过Tyr-残基的磷酸化减弱了与ZO-1蛋白的相互作用, 进而调节细胞的TJ完整性^[51]. 用展青霉素(patulin)作用于Caco-2结肠癌细胞后, ZO-1分子的磷酸化水平增加, 继而TJ结构被破坏, 导致肠上皮发炎、溃疡甚至出血^[52]. 降血钙素与其受体结合, 导致降血钙素受体和ZO-1相互作用和腺苷酸环化酶的活化, 腺苷酸环化酶激活蛋白激酶A, 进一步磷酸化ZO-1和Claudin-3, 导致TJ去装配, 促进前列腺癌侵袭^[53].

4 TJ在重要疾病中作用

4.1 TJ在肿瘤发展进程中的作用

肿瘤细胞的异常增殖、侵袭和转移是一个极其复杂的过程, 常伴随着TJ结构和功能的改变, 因此, TJ与肿瘤的发生发展密切相关. 目前发现, 许多TJ蛋白在肿瘤中呈异常表达, 例如, 与正常组织相比, ZO-1分子在结直肠癌中的表达显著降低, 发生肝转移时其表达进一步降低^[54]; 与正常乳腺上皮细胞比较, Claudin-3, -4在原发性乳腺癌中均有不同程度的上调^[55]; 免疫组化检测发现, Claudin-2在前列腺癌、乳腺癌中表达下调, 同时Claudin-3在肾癌、膀胱癌中以及Claudin-4在肾癌、肝癌中的表达也是下调的^[56]. 这些TJ蛋白的异常表达不仅改变了TJ的正常结构及功能, 也影响了肿瘤细胞的生物学行为, 增加了肿瘤的恶性程度, 加快了肿瘤的发病进程. 例如, Nasu等人^[57]发现, 肝细胞生长因子(hepatocyte growth factor, HGF)可以降低ZO-1分子的膜表达而增加其在胞浆中的表达, 进而增加了胃

上皮细胞的迁移能力. Soini等人^[58]发现, Claudin-7和-18的高表达与胰腺癌的肿瘤大小和分化程度相关; Todd等人^[59]发现, 过表达Claudin-3可促进乳腺癌细胞的迁移能力; Nordfors等人^[60]发现, Claudin-5在室管膜瘤中表达上调且与肿瘤的侵袭能力正相关; Takasawa等人^[61]发现, 胆道癌中Claudin-18与ERK信号通路间存在正反馈效应, 激活EGFR-ERK通路可上调Claudin-18的表达, 同时, 过表达Claudin-18也可以激活ERK信号通路, 这样的正反馈效应大大增加了肿瘤细胞的增殖和侵袭能力. 综上所述, 恶性肿瘤组织中的TJ蛋白的表达水平、细胞学分布或磷酸化状态的改变, 可引起TJ屏障的正常结构破坏, 从而导致肿瘤细胞增殖异常、分化变差、侵袭和转移能力增强.

TJ蛋白参与调控肿瘤增殖、侵袭和转移的调控机制已有一定的研究进展. 在肿瘤的增殖调控方面研究最多的是ZO-1蛋白. 作为第一个被发现的TJ胞浆蛋白, ZO-1不仅与维持和调节上皮细胞栅栏和屏障功能有关, 还参与调节细胞周期和增殖分化等重要过程. ZO-1相关核酸结合蛋白(ZO-1-associated nucleic acid binding proteins, ZONAB)是ZO-1相关的Y-box转录因子, ZO-1可以结合ZONAB并抑制其活性^[62]. ZO-1可通过上调增殖细胞核抗原(proliferating cell nuclear antigen, PCNA)、细胞周期蛋白cyclinD1和细胞周期蛋白依赖性激酶4 (cyclin-dependent kinase 4, CDK4)的转录促进G₁/S期细胞周期的转换, 促进细胞增殖^[63]. 下调ZONAB的表达或过表达ZO-1均可抑制CDK4的表达, 阻滞细胞周期, 进而抑制细胞增殖^[64]. 这些结果提示, ZO-1参与调控了上皮细胞的生长、分化及细胞周期进程.

在肿瘤的侵袭转移调控方面, TJ蛋白可通过影响MMP家族的基质降解酶活性、调节下游分子E-cadherin的表达等方式来调控肿瘤的侵袭和迁移. 基质金属蛋白酶(matrix metalloprotein, MMP)几乎能降解细胞外基质中的各种蛋白成分, 是肿瘤浸润和转移过程中主要的蛋白水解酶. 研究表明, ZO-1蛋白可调控膜型MMP (membrane type1-MMP, MT1-MMP)的表达, 敲除ZO-1会降低MT1-MMP在乳腺癌细胞中表达和体外三维侵袭^[65]. 在肝癌细胞中表达Claudin-1能增强基质金属蛋白酶2 (matrix metalloprotein, MMP2)的活性, 进而活化c-Abl-PKC信号通路, 促进侵袭和迁移^[66]. E-cadherin主要介导上皮细胞间的黏附, 近年来已成为肿

瘤细胞侵袭和转移的研究热点之一。研究表明, Claudin-7的表达缺失导致肿瘤细胞E-cadherin表达下调, 体外侵袭能力增加, 进而提高肺、结肠和食管癌等肿瘤的侵袭和迁移能力^[67-69]; 相反, 恢复表达Claudin-7可通过MAPK/ERK1/2途径降低HGF介导的侵袭和迁移^[69]。

4.2 TJ蛋白Claudin-1在丙肝病毒感染过程中的作用

丙肝病毒(hepatitis C virus, HCV)感染肝细胞是一个复杂缓慢的多步骤过程, Claudin-1是HCV进入肝细胞的必需宿主分子, 可作为共受体参与HCV的内化过程, 虽然Occludin蛋白也发挥一定作用, 但其作用过程尚不十分清楚^[70,71]。Belouzard等人^[72]将稳定表达CD81的HepG2细胞体外分化为有顶侧和基底侧向膜结构域的培养模型, 发现HCV可选择性感染基底侧向结构域, 病毒粒子也从该结构域释放。COP II囊泡成分Sec24C蛋白介导Claudin-1转运到细胞膜, 调控HCV进入^[73]。进一步的研究还表明, 人源靶向Claudin-1的单克隆抗体在持续性感染HCV的人肝嵌合体Upa-SCID小鼠中疗效显著^[74]。

4.3 TJ在遗传性耳聋发病机理中的作用

TJ使内耳内淋巴流和外淋巴流分离开, 以维持

内外淋巴流的离子稳态。相对于外淋巴流, 内耳内淋巴流有更高的电势和钾离子浓度。TJ蛋白的突变导致毛细胞退化, 在人和小鼠中引起遗传性耳聋^[75]。现已发现, *Claudin-7b*, *Claudin-9*, *Claudin-11*和*Claudin-14*基因突变与耳聋相关^[76-79]。*Tricellulin*是于2005年发现的首个位于三细胞连接处与耳聋相关的基因^[80]。

5 总结与展望

细胞TJ是物质经旁细胞途径转运的结构和功能基础, 双向参与细胞信号的调控, 不仅接收来自细胞内部的信号, 调控TJ蛋白的装配和成熟; 还可传递外来信号到细胞内部调控细胞的增殖、迁移、存活和分化。目前对TJ的表达、分布、结构和功能的研究较为丰富, 而对TJ的调控及其物质转运功能的分子机制研究相对滞后。目前研究表明, PKA, PKC, PKG及MAPK丝裂原活化蛋白激酶等上游激酶是参与调控TJ功能的重要信号分子, 阐明这些信号蛋白对TJ的调控机制将是今后研究的方向与重点。随着研究的深入, 对TJ在各类疾病的发生、发展及转归中的生物学功能, 以及TJ在肿瘤等相关疾病发生中的作用机制的深入阐明, 有助于对旁细胞物质转运的机制有更深入的了解, 并为探究多种疾病的发病机理, 进而通过人工调控旁细胞途径防治疾病提供新的思路。

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Research progress in the structure, assembly and functional regulation of tight junctions

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Tight junctions (TJs) are a type of multi-functional complex present in the most apical portion of the lateral plasma membrane of both epithelial and endothelial cell-cell junctions, and are mainly composed of transmembrane and cytoplasmic proteins. As a structural and functional basis, TJs are required to transport material through the paracellular pathway and responsible for maintaining apicobasal polarization. Additionally, TJs are involved in signal transduction bi-directionally. On the one hand, TJs receive signals from the cell interior and regulate assembly and maturation of TJs complex. On the other hand, TJs can also transmit external signals to the cell interior to modulate cell proliferation, migration, survival and differentiation. The present review mainly focuses on the latest research progress on TJs, including TJ's molecular architecture, assembly and its related regulatory mechanisms, as well as its biological function in tumorigenesis and development, hepatitis C virus infection and hereditary hearing impairment. We hope that the review may provide valuable reference for the future therapeutic strategies of epithelium-related disease by targeting TJs.

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