Hippo信号通路调控天然免疫的研究进展

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摘要 Hippo信号通路在细胞的增殖、分化以及凋亡等方面扮演着重要的角色. 同时Hippo信号通路又是响应多种环境条件的效应器, 如葡萄糖饥饿、细胞密度、病原体感染以及热激等. 近年来的研究发现, Hippo信号通路在天然免疫中具有重要的作用. 更为重要的是, Hippo信号通路在调控天然免疫过程中, 存在核心蛋白相互不依赖的特征, YAP(yes-associated protein)对天然免疫的调节往往独立于上游激酶的调控. 同时, 在不同的组织和物种中YAP的抵抗病原体的作用也存在差异. 本文从Hippo信号通路的演化、调控关系以及Hippo信号通路在抗病毒和抗细菌中的作用, 阐述了Hippo信号通路与自然免疫的关系.

关键词 YAP, 天然免疫反应, Hippo信号通路, TEAD

细胞增殖和分化的精确调控对维持组织稳态十分重要. 对Hippo信号通路的发现可以更好地理解生物体抑制器官过度生长的分子机制. 1995年, 在黑腹果蝇(*Drosophila melanogaster*)中首先发现Hippo信号通路中的一个同源NDR家族的蛋白激酶Warts(Wts)具有抑制组织过度生长的作用^[1,2]. 随后, 通过遗传学筛选在果蝇中发现一系列Hippo信号通路中的其他元件, 包括Salvador(Sav)蛋白^[3,4], 蛋白激酶Hippo(Hpo)^[5], 以及Mats(Mob as tumor suppressor)蛋白^[6]. 2005年, 通过酵母双杂交的方法发现, Hippo信号通路中最重要的转录因子辅助蛋白Yorkie(Yki). 遗传学证据和生化分析都表明, Hpo通过蛋白激酶Wts使Yki磷酸化失活^[7]. 随后的研究确定该信号通路的组件和功能在哺乳动物中高度保守^[8]. Hpo或Wts的功能缺失会导致果蝇相关器官的过度生长^[1,9].

例如, Hpo突变会导致果蝇眼球过度生长以及严重的头部折叠^[5]. 同样在组织器官再生中, Hippo信号通路的作用也发挥着重要作用. 例如, microRNA miR-302-367可以通过抑制LATS2(large tumor suppressor kinase)介导YAP的激活, 并促进小鼠心肌细胞的增殖和心脏的再生^[10]. 除了控制器官大小, Hippo信号通路还广泛参与癌症的发生发展^[11~13]. 最近的研究表明, Hippo信号通路在免疫调控中发挥重要的作用, 本文对最近相关的研究进行了综述.

1 Hippo信号通路

Hippo信号通路主要的三个元件分别是蛋白激酶Hpo/Mst, Wts/Lats以及YAP/Yki, 同时还包括一个广泛存在的含有TEA结构域的转录因子TEAD.

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1.1 Hippo信号通路的演化

Hippo信号通路最为核心的元件是转录因子辅助蛋白YAP/Yki, 因此YAP/Yki的保守性能够在一定程度上反映Hippo信号通路功能的保守性. 在后生动物海绵(*Amphimedon queenslandica*)、酵母(*Saccharomyces cerevisiae*)以及拟南芥(*Arabidopsis thaliana*)中并没有发现YAP的同源基因, 而在果蝇(*Drosophila melanogaster*)和丝盘虫(*Trichoplax adhaerens*)、海葵(*Nematostella vectensis*)、线虫(*Caenorhabditis elegans*)、海胆(*Echinoidea*)中YAP开始出现. 只有哺乳动物中同时具有YAP和Tafazzin(TAZ)两种功能同源的蛋白^[14,15](图1). 说明在有机体出现的18亿年以后YAP才首次出现^[16]. Hippo信号通路中的一个下游转录因子TEAD的出现明显早于YAP, 并在酵母和拟南芥中都存在^[14]. 在线虫中, Wts-1/Lats, YAP-1/YAP以及EGL-44/TEAD在信号调节上同源于哺乳动物^[15,17]. 虽然线虫中的serine/threonine-protein kinase(CST-1/2)同源于果蝇的Hpo, 但是其在功能上无法介导YAP的调控^[15,18]. 在哺乳动物中, YAP1蛋白丝氨酸127位点可以被LATS1/2磷酸化并和14-3-3蛋白相结合从而存在于细胞质中, 线虫中能够发挥相同磷酸化功能的丝氨酸位点在YAP-1的104位(图2).

1.2 Hippo信号通路的调控

Hippo信号通路开启时, 蛋白激酶Mst1/2通过磷酸化激活Lats1/2进而介导YAP/TAZ的磷酸化失活, 磷酸化的YAP与14-3-3蛋白结合滞留在胞质中^[19,20]. Hippo信号通路关闭时, YAP/TAZ实现去磷酸化的过程, 并进入细胞核中与转录因子TEAD结合, 转录调控下游的靶基因^[21].

哺乳动物中Hippo信号通路响应各种信号, 包括生长因子、接触抑制、应激压力、激素、营养、机械转导、细胞附着以及细胞极性等^[22]. 目前已知发现的调节Hippo信号通路的上游信号已经超过20种, 其中绝大多数与肠道稳态和癌症相关^[13]. 细胞的极化和细胞连接对Hippo信号通路的调节在肠道上皮细胞中表现得尤为明显. 肠道上皮细胞极性复合体可以调节Yap/Taz的转录水平, 此外参与细胞连接的蛋白AMOT, PTPN14以及 α -catenin可以直接与Yap/Taz发生相互作用^[21,23~25]. LKB1是细胞极性发育和维持的主要调控

图1 YAP和TEAD的演化
Figure 1 The evolution of YAP and TEAD

图2 秀丽隐杆线虫YAP-1和人类YAP蛋白的结构域示意图. TBD: TEAD结合区域. W: 包含2个保守的Trp残基的WW区域. 14-3-3BD: 14-3-3结合区域. S: 能够被LATS激酶磷酸化的丝氨酸

Figure 2 Domain structure of *Caenorhabditis elegans* YAP-1 and *Homo sapiens* YAP. TBD: TEAD-binding domain. W: WW domain containing two conserved Trp (W) residues. 14-3-3-BD: 14-3-3 binding domain. S: Serine residue for LATS kinase phosphorylation

者, 它可以通过其底物丝氨酸/苏氨酸蛋白激酶MARK和Scribble激活Hippo通路^[26], 还可以通过AMPK直接磷酸化YAP^[27,28].

营养缺乏、氧化应激、内质网应激以及缺氧都可以通过一系列的调节方式来调控YAP/TAZ^[29~31]. YAP/TAZ的活性还受到Rho GTPases和JNK1/2信号的抑制^[32]. 细胞外信号可以通过G蛋白偶联受体(G-protein coupled receptor, GPCR)调节Hippo信号通路. GPCR偶联的Gα12, Gα13, Gαq11可激活YAP/TAZ导致肿瘤发生^[33,34], 而Gαs的激活可以抑制YAP/TAZ的活性^[35].

2 Hippo信号通路在天然免疫和炎症中的作用

Hippo信号通路调节免疫的研究, 是近几年来对Hippo信号通路认识的一个全新的方面. 研究证明, Hippo信号通路在天然免疫和炎症反应都起着重要的作用.

2.1 Hippo信号通路与炎症的关系

YAP在内皮细胞中具有维持细胞稳态的作用, 不同的血流压力能诱发不同的细胞反应. Wang等人^[36]的研究表明, 内皮细胞中YAP/TAZ的磷酸化水平受不同的血流模式调节. 抑制YAP/TAZ可以抑制炎症的发生并延缓动脉粥样硬化形成, 而YAP的过表达可以诱导内皮细胞中促炎基因(如IL-6, VCAM1和ICAM1)等的表达. 在巨噬细胞中, 脂多糖(lipopolysaccharide, LPS)和II型干扰素(interferon- γ , IFN- γ)可以诱导IRF1, IRF5, IRF8, STAT1, STAT2以及NF- κ B等转录因子的激活, 促进M1巨噬细胞极化^[37]. 白细胞介素IL-4/IL-13诱导的M2巨噬细胞极化, 则是由另外的一群转录因子如IRF4, STAT6以及C/EBP β 等所调控^[38]. M1巨噬细胞在炎症和抗菌反应中起关键作用, 而M2巨噬细胞具有组织修复和抗炎的作用^[39]. 最新的研究结果表明, YAP抑制由IL-4/IL-13诱导的M2巨噬细胞极化, 同时促进LPS/IFN- γ 触发的M1巨噬细胞, 并诱导IL-6的产生^[40]. 以上结果说明, YAP在内皮细胞和巨噬细胞中正向调节炎症反应(图3).

2.2 Hippo信号通路在抗病毒中的作用

通常病毒核酸可以被模式识别受体所识别, 如Toll样受体(Toll-like receptor, TLRs)、NOD样受体(NOD-like receptor, NLRs)以及双链DNA细胞质感受器. 在内体中, TLRs用于识别病毒RNA和DNA^[41,42]. 病毒RNA受体RIG-I, 细胞溶质受体MDA5以及核苷酸转移酶cGAS则用于识别细胞质中的RNA和DNA^[43,44]. II型干扰素IFN- β 在抗病毒天然免疫反应中发挥着核心的作用, 可以有效地刺激各种先天和适应性免疫细胞, 包括巨噬细胞、NK细胞和T细胞. 最新研究表明, YAP在抗病毒天然免疫中发挥重要的作用. 病毒激活蛋白激酶IKK并促使YAP4在Ser403位点出现磷酸化, 从而导致溶酶体介导的YAP4降解. YAP4可以作为

图3 YAP在抗病原细菌侵染和炎症反应中的作用

Figure 3 Emerging roles of YAP in the inflammation and regulation of the innate immune response

IRF3激活的调节剂, 抑制IRF3介导IFN- β 的表达, 而且这一过程独立于蛋白激酶Hippo和LATS的调节^[45]. 与此相反的是, 磷酸化的IRF3可以稳定YAP-TEAD4复合体在细胞核内的结构^[46].

病毒诱导TBK1的活化所介导的病毒天然免疫反应涉及泛素化以及转录后修饰等过程. 在水泡性口炎病毒感染的早期, 细胞内核糖核蛋白复合体的形成促进TBK1的激活, 并诱导上皮细胞中IKK ϵ 的转录水平的升高^[47]. 此外, TBK1/IKK的活化依赖于Lys63连接的泛素化^[48]. Zhang等人^[49]的研究表明, 细胞营养和理化状态与抗病毒免疫密切相关, 这一过程主要是YAP/TAZ直接与TBK1结合并通过阻止TBK1 Lys63连接的泛素化来消除病毒诱导的TBK1活化. 说明YAP的不同亚型具有抑制抗病毒天然免疫的作用.

2.3 Hippo信号通路在抗病原细菌侵染中的作用

在哺乳动物中, 吞噬细胞是免疫系统重要的组成部分. 吞噬体通过细胞膜上的NADPH氧化酶产生活性氧物质(reactive oxygen species, ROS)杀死病原菌. 此外, 线粒体也可以产生大量的ROS. 周大旺课题组^[11]的研究表明, Hippo信号通路中的激酶Mst1和Mst2的缺失导致小鼠对败血症更加敏感. Mst1和Mst2通过促进小GTP酶Rac的激活, 完成TRAF6-ECSIT复合体的组装进而实现线粒体与吞噬体的融合并产生大量ROS. 此外, 结核分枝杆菌(*Mycobacterium tuberculosis*)诱导

激酶Mst1和Mst2磷酸化水平的提高,介导抗菌肽CXCL1和CXCL2的表达^[50]。在哺乳动物中,最近的一项研究表明,YAP-TEAD复合体的转录活性与免疫和炎症反应密切相关^[51]。在腹腔注射YAP-TEAD相互作用的抑制剂Verteporfin使得小鼠更容易被寄生虫鼠鞭虫(*Trichuris muris*)感染。另一方面,Pan课题组^[52]的一项研究表明,Hippo-Yki(Yap的果蝇同源直系物)信号通路,参与果蝇抵抗革兰氏阳性细菌感染。革兰氏阳性细菌感染激活果蝇脂肪体细胞中的Hpo和Wts,促进Yki从细胞核转位到细胞质,从而抑制了Yki的活性。RNAi沉默Hpo和Wts或过表达Yki均可导致果蝇对革兰氏阳性细菌感染的抵抗下降。因此,Yki在果蝇脂肪体细胞抵抗革兰氏阳性细菌中的天然免疫中起负调控作用。其作用机制是Yki和Scalloped(Sd)在转录水平促进Cactus(Ik β 的果蝇同源直系物)的表达,而Cactus通过阻止抑制NF- κ B家族成员Dorsal和Dorsal相关免疫因子DIF进核,从而抑制果蝇天然免疫反应(图3)。

嗜肺军团杆菌(*Legionella pneumophila*)作为细胞内病原菌可以产生一类异位效应蛋白(LegK)调节宿主的细胞进程。异位效应蛋白LegK1可以刺激NF- κ B的激活^[53],LegK2通过磷酸化ARP2/3复合物的ARPC1B和ARP3亚基,并导致肌动蛋白细胞骨架重塑^[54]。Lee等人^[55]研究发现,异位效应蛋白LegK7可以诱导MOB1的磷酸化,导致YAP1/TAZ磷酸化水平的提高进而降解,从而改变巨噬细胞的转录谱,实现对Hippo信号通路的劫持。最终嗜肺军团杆菌在巨噬细胞内大量增殖。这一过程表明,非磷酸化的YAP1/TAZ在细胞核内的转录调控作用有利于巨噬细胞抵抗嗜肺军团杆菌的侵袭。

Hippo信号通路从低等的秀丽隐杆线虫到高等的哺乳动物具有高度的保守性。在线虫中,*yap-1*的缺失

致使线虫寿命的延长以及对高温的敏感性增加^[15]。由于高温可以促进线虫表皮组织YAP-1的激活,因此YAP-1正调控线虫抵抗高温^[15]。线虫中同源于哺乳动物LATS蛋白的WTS-1对YAP-1的调节十分保守,而WTS-1通过调节顶端肌动蛋白的定位影响线虫肠道顶膜的完整性^[56]。Hippo信号通路的下游转录因子EGL-44/TEAD主要表达在线虫的运动神经元、表皮以及肠道中^[57],EGL-44通过结合EGL-46调控FLP神经元的分化^[57,58]。FTT-2/14-3-3蛋白同样可以和YAP-1结合,并使磷酸化的YAP-1滞留在细胞质中^[15]。本实验室最近的研究发现,在线虫和小鼠肠道中,细菌侵袭破坏肠道屏障和细胞连接,导致YAP-1由胞浆转位进核。YAP-1进核激活转录因子EGL-44介导的转录,调控一系列和免疫反应相关的基因,从而帮助线虫和小鼠抵抗细菌对肠道的侵袭(马怡诚等人,结果未发表)。本研究表明,YAP-1在肠道细胞抵抗细菌感染过程中起正调控作用(图3)。因此,YAP在不同类型的组织中发挥不同的天然免疫和炎症作用。

3 总结与展望

Hippo信号通路是一条极其保守的信号通路,转录辅助因子YAP可以与TEAD以外的多种转录因子相互结合。有趣的是,Hippo信号通路中的不同激酶对天然免疫的调控相互独立;同时,YAP对天然免疫的调节存在组织差异性,影响这一差异性的原因可能与细胞连接有关。YAP细胞分布在不同组织中存在差异性,这一因素会直接影响YAP在天然免疫中所扮演的角色。在线虫以及哺乳动物中转录因子TEAD同样存在多种亚型;在天然免疫中,TEAD是否也有功能的分化以及是否有独立于YAP以外的蛋白可以作为TEAD的激活因子仍然需要进一步的研究。

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Hippo signaling pathway regulation of innate immune response

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The Hippo signaling pathway plays crucial role in cell proliferation, differentiation, and apoptosis. Furthermore, it acts as a sensor that responds to a variety of environmental conditions, such as glucose starvation, cell density, pathogen infection, and heat shock. Recent studies have revealed that the Hippo signaling pathway is involved in innate immunity. More importantly, this pathway is characterized by the mutual independence of core proteins to regulate innate immunity. In this pathway, the regulation of innate immune response by Yes-associated protein (YAP) is often independent of the large tumor suppressor kinases or mammalian STE20-like kinases. There are further differences in YAP mediation in regulating the innate immune response against pathogens in different tissues and species. In this review, we summarize the evolution and regulation of the Hippo signaling pathway and its role in antiviral and antibacterial defense mechanisms.

YAP, innate immune response, Hippo signaling pathway, TEA domain transcription factor (TEAD)

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