综 述

Notch信号与心脏干细胞关系的研究进展

蒋晓帆 丁然然 姜汉国* 揭 伟*

(广东医学院基础医学院病理学教研室, 湛江 524023)

摘要 Notch信号是广泛存在于各种动物细胞中高度保守的信号途径, 在干细胞生物学功能中发挥重要作用。心脏干细胞(cardiac stem cells, CSCs)是存在于心脏特殊微环境下的多潜能干细胞, 其表面存在Notch受体, 而与其相邻的细胞可表达Notch配体, 提示心脏干细胞中的Notch信号在某些条件下可被活化。该文从Notch信号通路的组成和激活、CSCs的界定与来源、CSCs主要类型的一般生物学特征及Notch信号通路与CSCs形成、分化和增殖的关系等方面进行综述, 并展望了基于CSCs在心肌再生相关转化医学研究中的前景。

关键词 Notch信号; 心脏干细胞; 起源; 分化; 增殖; 心肌再生

Research Update of Relationship between Notch Signaling Pathway and Cardiac Stem Cells

Jiang Xiaofan, Ding Ranran, Jiang Hanguo*, Jie Wei*

(*Department of Pathology, School of Basic Medicine Sciences, Guangdong Medical College, Zhanjiang 524023, China*)

Abstract Notch signaling is a highly conserved signaling pathway in a wide variety of animal cells, which plays an important role in stem cells biology. Cardiac stem cells (CSCs) are multipotent cells which locate in the niche of heart. Notch receptors are distributed on the CSCs membrane and the neighboring cells express Notch ligand, suggesting Notch signaling in CSCs could be re-activated under certain conditions. In the present paper, we reviewed the composition and activation of the Notch signaling pathway, the definition and origin of CSCs, the general biological characteristics of the main types of CSCs and the relationship between Notch signaling pathway and the formation, differentiation and proliferation of CSCs, as well as the perspectives of CSCs in the myocardial regeneration by CSCs transplantation.

Key words Notch signaling pathway; cardiac stem cells; origin; differentiation; proliferation; myocardial regeneration

Notch信号通路广泛存在于脊椎动物和非脊椎动物, 在进化上高度保守, 通过相邻细胞之间的相互作用而活化, 在调节细胞、组织、器官的分化和发育上起重要的作用。心脏干细胞(cardiac stem cells, CSCs)又称心脏祖细胞(cardiac progenitor cells, CPCs), 是存在于心脏特殊微环境下的多潜能干细胞, 具有分化为心肌细胞、平滑肌细胞和内皮细胞的潜能。有关CSCs移植在缺血性心脏疾病治疗中的研究受到极大的重视, 相关的转化医学研究进展迅速, 然而有关CSCs形成、分化和增殖等的调控机制尚有待于进一步阐明。鉴于Notch信号通路与干

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*通讯作者。Tel: 0759-2388584, E-mail: JIANGHG@163.com; Jiewei74@126.com
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*Corresponding authors. Tel: +86-759-2388584, E-mail: JIANGHG@163.com; Jiewei74@126.com
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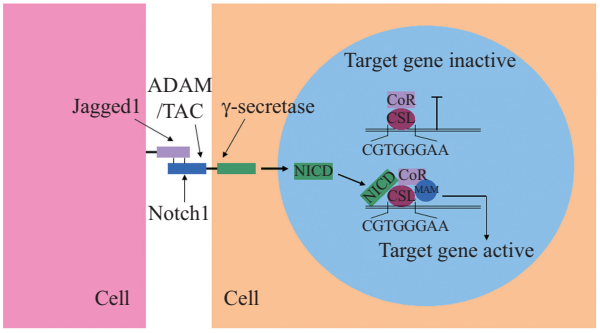
细胞生物学功能密切相关, 阐明Notch信号与CSCs之间的关系将为基于CSCs的心肌再生转化医学研究提供参考。

1 Notch信号通路组成和激活

美国遗传学家Thomas Hunt Morgan于1917年描述了一种果蝇突变体, 其特点是翅膀末端出现锯齿状缺损。1983年, 调控该果蝇翅膀末端出现锯齿状缺损的*Notch*基因被克隆。研究发现, Notch是一类在进化上高度保守的受体蛋白, 该信号通路主要包括Notch受体、配体、CSL DNA结合蛋白以及效应分子[1-2]。果蝇中存在1种Notch受体(Notch)及2种Notch配体(Delta和Serrate), 而哺乳动物有4种Notch受体(Notch1、Notch2、Notch3和Notch4)和5种Notch配体(DII1、DII3、DII4、Jaggedl和Jagged2)。Notch信号效应分子主要为HES, 该家族有6个成员, 其中HESl和HES5在Notch通路中发挥作用。Notch配体和受体都是I型单跨膜蛋白, 信号通讯被限于相邻细胞间进行, 需要细胞之间的相互接触才能激活。Notch受体蛋白由胞外区、跨膜区和胞内区组成, 其中胞内区和胞外区均为高度保守区域, 胞外区是结合配体并激活受体的部位, 由29~36个表皮生长因子(EGFR)样重复序列组成, 其中第11、12个EGFR样重复序列介导与配体的结合。Notch的胞内区(Notch intracellular domain, NICD)则由多个功能结构域组成: 1个N-端RAM结构区、6个细胞分裂周期基因10(cell division cycle gene 10, CDC10)重复序列、2个核定位信号(nuclear localization signal, NLS)、1个转录激活区和富含PEST序列(proline, glutamic acid, serine and threonine-rich sequences)的结构域[3]。Notch配体又名DSL(Delta, Serrate, Lag2)蛋白, 其配体有两类, 一类是Delta样配体, 分别是Dll1、Dll3、Dll4; 另一类是Serrate样配体, 分别为Jaggedl和Jagged2[4]。Serrate样配体有一个富含半胱氨酸区域, 而Delta样配体则无此区域。在缺乏配体结合时Notch受体以非活化形式存在, 而Notch受体和配体结合后发生两次剪接, 第一次剪接由ADAM家族的蛋白酶肿瘤坏死因子转化酶(TNF-alpha converting enzyme,TACE)介导, 第二次剪接由γ-分泌酶催化, 释放出NICD。NICD转运至核内是激活Notch下游信号的关键, 当核内缺乏NICD时, CSL能特异性地结合核内DNA序列CGTGGGAA, 从而抑制下游基因的转录, Notch信号激活后, 释放的NICD转运到细胞核并与CSL结合(人体为CBF-l, 大鼠为RBP-J, 果蝇为Suppressor of Hairless, 线虫为LAG1, 其为Notch信号通路的初级效应分子), CSL通过置换辅助抑制物使其由抑制剂转变为激活剂, 并招募共激活因子, 如操纵子样蛋白(mastermind/Lag-3, MAML), 从而发挥一系列生物学作用。碱性螺旋–环–螺旋(bHLH)家族转录因子是Notch信号途径最主要的靶标, 哺乳动物中至少有2个bHLH蛋白家族能被Notch诱导表达: 一是HES(hairy/enhancer of split)家族, 二是HRT(hairy related transcription factor)家族。这些转录因子能够进一步调控下游分子的表达[5]。图1以Notch1活化为例示意Notch信号激活的机制。



Notch1受体与Jagged1配体结合后, 经过ADAM/TAC和γ-secretase酶剪切释放的NICD进入细胞核内, 与CSL形成蛋白复合物, 继而使共抑制因子(CoR)转变为共激活因子, 随后在其他因子如MAM的辅助下激活靶基因(*HES*和*HRT*基因)转录。

Notch1 receptor binds with its ligand Jagged1, then releases the NICD into the nucleus via sequential cleavage by ADAM/TAC and γ-secretase. NICD forms a protein complex together with CSL and then turns the co-repressor (CoR) into co-activator, subsequently to activate transcription of target genes (*HES* and *HRT* genes), with presence of other factors such as MAM.

图1 Notch1信号活化机制示意图

Fig.1 Schematic overview of the Notch1 signaling pathway

2 心脏干细胞(CSCs)

2.1 CSCs界定及来源

传统观念认为, 心脏在出生时包含一定预定数量的心肌细胞, 细胞死亡后不能再补充, 这主要与心肌细胞是一种终末分化细胞理念相吻合。然而近10年来系列的研究表明, 心脏中存在一定数量的、类型各异的CSCs, 因而提示细胞移植治疗心肌损伤具有可能性[6]。CSCs具有自我更新、克隆增殖及分化为心脏结构细胞的能力, 可在心肌损伤后通过迁移来参与心脏损伤修复, 提示心脏的完整性可能由CSCs的数量及功能来维持[7]。关于CSCs的来源有

两种理论, 一是CSCs来源于胚胎时期存在于心脏中的内源性细胞, 这种CSCs可表达胚胎干细胞标志物Islet-l。第二是CSCs来源于出生后外源性细胞如髓系干细胞定植于心肌内的细胞。在成年个体中, 心脏干细胞主要包括骨髓源心脏干细胞、循环心脏干细胞和组织心脏干细胞, 组织心脏干细胞主要是指定位于心肌组织内的心肌干细胞。

2.2 CSCs类型及一般生物学特征

根据细胞表面标志物和定位的不同, 心脏组织中存在不同类型的CSCs。国内外研究人员对CSCs进行了初步的概括[6,8-12], CSCs主要包括如下几个类型。

2.2.1 $Lin^-/c\text{-}kit^+$细胞 $Lin^-/c\text{-}kit^+$细胞是最早发现的一群CSCs, 是成体心肌组织中数量最多的干细胞类型, 约每10^4个心肌细胞中就有1个$Lin^-/c\text{-}kit^+$ CSC。2003年, Beltrami等[13]在成年大鼠心脏内分离出一种$Lin^-/c\text{-}kit^+$细胞, 这些细胞成簇地分布于心尖、心房和心室基中部(base-midregion)区域[14], 该细胞表达心肌转录因子GATA4、Nkx2.5和MEF2, 但不表达血细胞系表面标记物(CD34、CD45、CD20、CD45RO、CD8和TER-119)及平滑肌细胞、内皮细胞、成纤维细胞的标记物蛋白。$Lin^-/c\text{-}kit^+$细胞在体外可自我克隆和增殖, 并能分化为心肌细胞、平滑肌细胞和内皮细胞, 因而具有成体干细胞相似的特性。最近, Bolli等[15]报道了一项I期临床试验, 结果证实, 心肌梗死后体内移植$Lin^-/c\text{-}kit^+$ CSCs可缩小梗死面积, 从而改善心功能。

2.2.2 $Sca\text{-}l^+$细胞 2003年, Oh等[16]在成年小鼠心脏组织内发现一种$Sca\text{-}1^+$干细胞, 是位于心室基底部附近的一群小细胞。与$c\text{-}kit^+$细胞不同的是, $Sca\text{-}l^+$细胞并不表达Nkx2.5, 但表达心肌其他转录因子, 如GATA-4、MEF-2C和TEF-1。Matsuura等[17]证实, $Sca\text{-}l^+$ CSCs经体外诱导后可分化为心肌细胞。心肌梗死动物移植$Sca\text{-}1^+$ CSCs后能提高其心功能, 表现为左室射血分数(LVEF)上升, 左室舒张末期容积(LVEDD)减少, 左室收缩末期容积(LVESD)减少[18]。

2.2.3 SP细胞 SP细胞又称边集细胞或侧群细胞, 是近年来在多种不同种属哺乳动物心脏中发现的一类心肌前体细胞, 约占心脏细胞的1%[19]。对SP细胞的表型分析显示, 其Sca-1、c-kit、CD34、Flk-2和Thy1.1呈低表达。通过尾静脉将SP细胞移植到心肌梗死的动物体内, SP细胞可归巢入心脏并分化为心肌细胞、心脏血管平滑肌细胞和血管内皮细胞, 提示SP细胞具有修复损伤心肌组织的潜力[20]; 直接心肌内注射SP细胞也证实具有相似的分化功能[21]。

2.2.4 心肌球样细胞 2004年, Messina等[22]从哺乳动物的心房和心室中分离出一种称为CDCs(cardiosphere cells, 心肌球样细胞)的干细胞, 是一种具有自我更新、克隆和多能分化特性的干细胞, 体外可分化成心肌细胞、平滑肌细胞和内皮细胞。CDCs表达干细胞相关抗原c-kit、CD34、CD31、$CD45^+$、Sca-1、Nkx2.5、GATA4、cTnI和α-sarcomeric actin[23]。新近报道的一项I期临床试验结果证实, CDCs移植能减小心肌梗死灶疤痕面积并增加左室射血分数[24]。

2.2.5 $Islet\text{-}1^+$细胞 Laugwitz等[25]在新生小鼠、大鼠和人的心脏中发现了另一种未分化的$Islet\text{-}1^+$细胞。在新生哺乳动物的心脏中, $Islet\text{-}1^+$细胞主要分布在流出道、心房和左心室。该细胞表达Nkx2.5和GATA4, 不表达Sca-1、CD31及c-Kit。$Islet\text{-}1^+$细胞仅能从比较年轻的个体中得到, 在成年个体心脏中数量显著减少。Moretti等[26]研究证明, 乳鼠心脏中$Islet\text{-}1^+$细胞在体外能够分化为血管内皮、平滑肌、心内膜、传导系统、右室及左房肌细胞谱系。$Islet\text{-}1^+$细胞能否在成体心脏中分离、扩增并分化为心肌细胞尚不清楚。

2.2.6 心外膜源性前体细胞 2004年, Wessels等[27]提出心外膜源性前体细胞(epicardium derived progenitor cells, EDPCs)可能为CSCs。2007年, Winter等[28]从成人心房组织中分离出人EDPCs, 该细胞表达α-SMA、vWF、SERCA2a和SCN5a, 而不表达cTnI、sarcomeric myosin或α/γ-muscle actin。EPDCs具有多向分化能力, 体外可分化为成纤维细胞、内皮细胞和血管平滑肌细胞[29]及心肌细胞[30]。也有报道显示, 体内移植的EPDCs并未分化为心肌细胞, 其主要是通过旁分泌作用提高心肌梗死后的心功能[31]。

2.2.7 $SSEA\text{-}1^+$细胞 Ott等[32]从大鼠心脏中分离出一种新型干细胞, 其表达胚胎干细胞相关标志物$SSEA\text{-}1^+$。新生大鼠$SSEA\text{-}1^+$细胞同时表达Nkx2.5、GATA4和sarcomeric myosin, 但是在成熟大鼠心脏缺乏相应心脏特异标志物的表达。在体外, $SSEA\text{-}1^+$细胞可分化为心肌细胞、平滑肌细胞和内皮细胞; 大鼠心肌梗死后2周, 心肌梗死灶局部注射$SSEA\text{-}1^+$心脏干细胞, 移植的细胞表达sarcomeric myosin、Con-

nexin43及vWF, 提示该细胞可以向心肌细胞和血管内皮细胞分化, 移植细胞组心肌梗死面积缩小, 心脏收缩功能提高。

2.2.8 Nkx2.5$^+$细胞 Wu等[33]从小鼠胚胎心脏中分离出了一群Nkx2.5$^+$细胞, 它们中的大多数可以分化为心肌细胞和传导系统细胞, 有些甚至可以分化为平滑肌细胞。

上述从人或不同种属动物心脏中分离出的CSCs表面标志物不同间或有重叠, 生物学功能上或有差异。对于心脏组织中的CSCs, 究竟它们的起源如何, 尚有争议。此外, 对于上述不同类型CSCs的生物学关系, 尚有待于进一步明确。国内外大多数研究者更多关注c-kit$^+$ CSCs[34-42]。目前, c-kit$^+$ CSCs和CDCs已进入I期临床试验[15,24]。表1概括了当前报道的心肌组织源性CSCs的特征。

3 Notch信号与CSCs生物学之间的关系

Notch信号活化介导的干细胞生物学功能存在明显的差异。信号活化时间的不同、信号抑制剂的浓度差异及细胞微环境的不同, Notch所产生的效果也不同, 甚至可能导致截然相反的结果[43-46]。Notch信号在哺乳动物心脏胚胎发育期起着重要作用, 参与心肌分化的调节, 调控心脏各结构的形成。和许多胚胎蛋白的表达一样, Notch信号在出生后的心脏中的表达水平明显降低。Notchl/Jaggedl可使早期心肌细胞免遭凋亡, 随着心肌细胞发育成熟, Notchl信号强度逐渐减弱, 而心肌增殖能力也明显下降。在受损和再生的组织如脑、肝脏、胰腺和血管中, Notch信号可重新激活[47-52]; 在成体心脏中, 条件性激活Notch能对心脏起保护作用, 而抑制Notch信号将加重心梗的恶化[53-55]。在受损的成年心脏组织中, Notch信号再激活主要参与心肌细胞凋亡和CSCs分化之间的动态平衡, 调节CSCs增殖和分化, 促进损伤心肌的修复, 从而维持心肌组织稳态。

3.1 Notch信号与CSCs形成

研究显示, TGF-β1刺激通过上皮间叶转化

表1 不同类型心脏干细胞特征

Table 1 The characteristics of different subtypes of cardiac stem cells

类型 Type	表型 Phenotype	定位 Location	体外分化 Differentiation *in vitro*	体内生物学功能 Biological function *in vivo*	参考文献 References
Lin$^-$/c-Kit$^+$ cells	c-Kit$^+$, GATA4$^+$, Nkx2.5$^+$, MEF2$^+$, Lin$^-$, α-SA$^-$, CM$^-$, α-CA$^-$, vWF$^-$, Fibronectin Procollagen I$^-$, α-SMA$^-$	Atria, apex and base-midregion of the ventricle	Myocardiocytes, smooth muscle cells, vascular epithelia cells	LV systolic function ↑, infarct size ↓	[13-15,34-42]
Sca-l$^+$ cells	Sca-1$^+$, GATA-4$^+$, TEF-1$^+$, MEF-2C$^+$, CD31$^+$, CD38$^+$, Lin$^-$, c-Kit$^-$, Nkx2.5$^-$, CD34$^-$, CD45$^-$	Adjacent to the basal lamina of the heart	Myocardiocytes	LV systolic function ↑	[16-18]
SP cells	Sca-1$^-$, c-Kit$^-$, CD34$^-$, Flk-2$^-$, Thy1.1$^-$	Perivascular area and interstitial space of heart	Myocardiocytes, smooth muscle cells and vascular epithelia cells, osteocytes and adipocytes	ND	[19-21]
CDCs	c-Kit$^+$, CD34$^+$, CD31$^+$, Sca-1$^+$, CD45$^+$, Nkx2.5$^+$, GATA4$^+$, α-SA$^+$, cTnI$^+$	Atria and ventricular	Myocardiocytes smooth muscle cells and vascular epithelia cells	Scar size ↓, regional function ↑, viable myocardium ↑	[22-24]
Isl1$^+$ cells	Nkx2.5$^+$, GATA4$^+$, Sca-1$^-$, CD31$^-$, c-Kit$^-$	Out flow tract, left ventricle and atria	Myocardiocytes, smooth muscle cells and vascular epithelia cells	ND	[25-26]
EDPCs	α-SMA$^+$, vWF$^+$, SERCA2α$^+$, SCN5α$^+$, cTnI$^-$, CM$^-$, α/γ-muscle actin$^-$	Atria	Smooth muscle cells and vascular epithelia cells, cardiomyocytes and fibroblasts	LV systolic function ↑	[27-31]
SSEA-1$^+$ cells	Nkx2.5$^+$, GATA4$^+$, Desmin$^-$	ND	Cardiomyocyte, endothelial and smooth muscle	ND	[32]
Nkx2.5$^+$ cells	c-Kit$^+$, CD34$^+$, CD31$^+$, Sca-1$^+$, CD45$^+$, Nkx2.5$^+$, GATA4$^+$, α-SA$^+$, cTnI$^+$	ND	Myocardiocytes, vascular epithelia cells and transduction system cells	ND	[33]

α-SA: α-横纹肌肌动蛋白; CM: 心肌肌球蛋白; α-CA: α-心肌肌动蛋白; α-SMA: α-平滑肌肌动蛋白; LV: 左心室; ND: 未确定。

α-SA: α-sarcomeric actin; CM: cardiac myosin; α-CA: α-cardiac actin; α-SMA: α-smooth muscle actin; LV: left ventricle; ND: undetermined.

(EMT)的机制诱导CDCs的产生[56], 而Notch信号与EMT有关, Notch信号对心脏发育的重要性已得到很好的阐明[57-58], 但目前尚不清楚Notch信号对胚胎时期心脏发育过程中CSCs的产生有何作用。最近, Zakharova等[59]报道, Notch1信号活化促进成年大鼠心外膜源性c-Kit$^+$ CSCs发生EMT而调节其增殖, 而抑制Notch1信号能维持c-Kit$^+$ CSCs的多能性; 在体外培养条件下, Jagged1$^+$/c-Kit$^-$ CSCs与Notch1$^+$/c-Kit$^+$ CSCs相互接触活化了Notch1信号进而调节CSCs的形成。

3.2 Notch信号与CSCs分化

配体和受体的存在及有效结合是Notch信号得以活化的关键因素。处于心脏干细胞微环境中的c-kit$^+$ CSCs表面主要表达Notch1受体, 其周围的细胞表达Jagged1配体, CSCs与相邻细胞接触后Notch信号将被激活, 活化的Notchl直接调控CSCs中Nkx2.5的启动子活性, 正性调节c-kit$^+$ CSCs分化为心肌细胞[55]。此外, Urbanek等[53]进一步证实, 通过强制表达N1ICD而活化Notch1信号亦可促进c-kit$^+$ CSCs分化为心肌细胞。相反, 用Notch信号阻断剂如DAPT处理梗死的心脏, 阻止了CSCs分化为心肌细胞, 显著减弱CSCs的定向分化能力, 从而导致心脏修复障碍[55], 甚至发展为扩张性心肌病, 而停止使用DAPT, 心脏的再生功能得以恢复[53]。新近, Matsuda等[36]报道人c-kit$^+$ CSCs在低密度(340细胞/cm^2)培养时可较好维持其未分化状态, 而在高密度(5 500细胞/cm^2)培养时易活化Notch信号从而自我分化为内皮细胞; 同时, 体内移植低密度培养的CSCs或高密度培养联合Notch信号抑制剂处理的CSCs均能获得较好的心肌分化和心功能改善效果[36], 这从另一个角度提示Notch信号活化时间和空间的差异对CSCs分化能力和方向具有重要的影响。

心肌梗死区血管系统的受损将直接威胁生物体的生存。重建心梗区的脉管系统使心脏重新获得氧和营养物质, 是维持心脏活性的最为关键的一步[60-62]。Chen等[63]首次研究证实, Notch信号通过RBPJ依赖的信号途径激活而促进CDCs分化为血管平滑肌细胞, 抑制大鼠CDCs的RBPJ表达显著降低CDCs向平滑肌分化; 而体内植入过表达NICD的CDCs向平滑肌分化的数量明显增多, 提示Notch1信号活化可促进CDCs参与心梗后血管新生。然而, Notch1信号活化诱导CDCs分化的细胞并非全部表达平滑肌细胞标志物, 同时也表达血管内皮细胞和心肌细胞标志基因, 提示Notch活化可以调节CDCs多向分化[63]。

总之, 现有的资料表明, 活化的Notch信号能有效刺激CSCs分化为心肌细胞、平滑肌细胞和内皮细胞, 参与受损心肌组织的重建而修复心功能。

3.3 Notch信号与CSCs增殖

Notch信号活化可促进CSCs的增殖。Nemir等[64]等通过构建心肌细胞特异性过表达*Jagged1*转基因小鼠, 发现新生*Jagged1*转基因小鼠心脏中NKX2.5$^+$ CSCs持续增殖, 成年后该转基因小鼠心肌细胞数量多于对照组; 同时还发现, *Jagged1*转基因小鼠在心脏应激条件下Sca-1$^+$/NKX2.5$^+$ CSCs增殖明显。

3.4 Notch信号与其他信号的相互交流对CSCs生物学功能的影响

除了直接影响CSCs生物学功能, Notch信号还通过与其他信号的相互交流(crosstalk)来发挥间接的影响。Klaus等[65]研究证实, Wnt/β-catenin和BMP信号可作为Notch/RBPJ信号下游分子在小鼠胚胎CSCs不同分化阶段起作用。Notch1信号通过磷酸化β-catenin而抑制β-catenin介导的Islet-1$^+$ CSCs的增殖, 进而调节其分化[66]。PI3K/Akt信号在CSCs迁移[67-69]、分化[70]、体内移植存活[71]等事件中发挥重要作用。我们的最新结果也显示, PI3K/Akt信号在SCF/c-Kit信号介导的c-Kit$^+$ CSCs体外迁移中发挥重要作用[72]。在巨核细胞分化过程中, Notch与PI3K信号存在相互交流[73], 在CSCs中Notch与PI3K信号是否也存在相互交流, 尚缺乏报道。

4 结语与展望

Notch信号作为生物体进化过程中保守的信号途径, 对于其组成和活化的调节机制目前研究较为完善, 但Notch信号的生物学功能具有时间和空间特异性, 这种特异性的本质尚缺乏相应理论模式和动物模型来阐明。鉴于目前报道的CSCs种类繁多, 究竟各类型细胞之间的生物学关系如何, 尚不清楚。如此众多的CSCs类型, 哪些类型才是真正意义的心脏源性干细胞? 这一问题也有待于今后进一步明确。尽管当前有关CSCs的研究提示, Notch信号活化可促进其多向分化而参与受损心肌组织的重建, 但Notch信号影响CSCs形成、存活、分化和增殖的机制还有待于进一步深化, 特别是Notch信号对上述不

同类型CSCs生物学功能影响的差异性研究尚未见报道; 此外, Notch信号与其他如Wnt/β-catenin、BMP、PI3K/Akt及Hedgehog等众多的与干细胞功能密切相关的信号之间的相互交流, 应得到更为详尽的阐明。当前, 基于CSCs移植治疗缺血性心脏病已成为心血管疾病研究中的热点, 特别是近期报道的几项CSCs移植治疗缺血性心脏病的I期临床试验的结果更是鼓舞人心[15,24], 因此, 深入地认识Notch信号与CSCs生物学功能的关系, 将会极大地推进基于移植CSCs治疗心肌梗死等缺血性心脏病相关转化医学的进展。

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