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述评 EDITORIAL

胃肠平滑肌起搏功能研究的最新动态

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Advances in research on pacemaking function of gastrointestinal smooth muscle cells

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Abstract
Gastrointestinal smooth muscle has spontaneous contractile activity, which is very important to digestion and absorption function. However, the pacemaking mechanism in gastrointestinal smooth muscle is still not clear. In this article, we review the recent advances in research on the mechanisms underlying gastrointestinal pacemaker activity. We summarize the classification, function and pacemaking mechanisms of pacemaker cells, and the relationship between pacemaker cells and gastrointestinal motility dysfunction. As abnormal pacemaking activity is often associated with gastrointestinal motility dysfunction, it is of great clinical significance to clarify the pacemaking mechanisms in the gastrointestinal tract.

Key Words: Gastrointestinal tract; Interstitial cell of Cajal; Pacemaker current; Gastrointestinal motility disease

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摘要
胃肠道平滑肌具有自动节律性收缩的特性, 对消化和吸收功能具有十分重要的生理意义, 但目前尚未明确胃肠道平滑肌的起搏机制. 本文综述了近几年关于胃肠道起搏机制研究的最新进展, 从起搏细胞的分类、功能、起搏机制以及其与胃肠动力障碍性疾病的关系等方面做了阐述. 胃肠道平滑肌起搏活动的异常是引发胃肠动力障碍性疾病的重要原因之一, 因此, 胃肠起搏机制的相关基础研究具有重要的临床意义.

关键词: 胃肠道; Cajal间质细胞; 起搏电流; 胃肠动力障碍性疾病

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0 引言
胃肠道平滑肌具有自发性、节律性蠕动的特性, 类似心脏节律性的起搏活动, 这种自发节律性运动由慢波(slow wave), 即基本电节律(basic electric rhythm)控制. 胃肠道平滑肌的自发节律性运动对机体的消化和吸收功能具有非常重要的生理意义. 目前, 消化系平滑肌的起搏机制以及起搏功能异常导致的动力障碍性疾病的发病机制还有许多问题需要解决. 近十年来, Cajal间质细胞(interstitial cells of Cajal, ICC)成为胃肠起搏功能机制和一些胃肠动力障碍性疾病研究的热点细胞, 从而引起基础和临床研究领域学者们的广泛关注. 本文以基础和临床研究的最新科研成果为背景阐述了胃肠平滑肌起搏功能机制以及相关疾病的研究进展.

1 胃肠道起搏细胞的分类及功能
Ambache等[1]首次发现慢波电节律控制小肠收

■背景资料
关于胃肠Cajal间质细胞的研究已有一百多年的历史. ICC作为胃肠起搏细胞不仅产生慢波电活动, 将电信号传递给平滑肌, 还参与胃肠动力功能的调节, 因此日益得到学者们的广泛重视. 近年来, 有关胃肠ICC的分布以及形态学的研究已较清楚, 但关于ICC起搏功能的研究还存在多种争议和无法解释的现象.

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■研发前沿
胃肠动力相关疾病一直是临床常见病、多发病, 因其复杂多样给临床治疗带来一定困难. 对ICC的研究使人们逐渐意识到ICC的结构和功能异常是导致胃肠动力疾病的关键因素, 因此ICC将成为胃肠动力疾病治疗的关键和靶点.

缩活动, 并发现慢波的产生与存在于肠道平滑肌间的ICC有关. 从此, ICC与慢波之间的关系得到深入研究. 根据所在部位不同, 将存在于胃肠道内的ICC分为4类[2], (1)ICC-MY: 位于环形肌和纵形肌之间; (2)ICC-IM: 位于肌束间; (3)ICC-DMP: 位于环形肌深肌层内的ICC-IM, 只存在于小肠; (4)ICC-SM: 位于黏膜下层, 只存在于结肠. 现有的研究结果表明, ICC-MY和ICC-IM两种细胞与胃肠道平滑肌的自发性收缩活动有关. ICC-MY是主要的起搏细胞, 具有自动产生节律性去极化的功能, 从而产生慢波[3,4]. ICC-MY作为起搏细胞产生的自发性内向电流称之为起搏电流. ICC-IM同样能够产生一种持续性放电活动, 称之为单位电位(unitary potentials), 依靠这种电位的存在, ICC-IM可将ICC-MY产生的起搏信号传递给予ICC-IM形成紧密连接的平滑肌[5], 从而完成自发性收缩过程, 除此之外, ICC-IM在神经信号传递过程中还具有调节作用[6]. 由此可见, ICC-MY和ICC-IM在胃肠道慢波的产生、传递及神经肌肉信号传递的过程中承担着不同的功能.

2 起搏电位产生的机制

“起搏单位”是ICC-MY产生自动去极化的关键结构, 由IP3敏感的钙库、线粒体及钙敏感的通道三部分组成[7-10], 即首先发生IP3Ⅰ型受体的激活, 使IP3敏感的钙库释放钙[9,10], 随后引发线粒体摄取钙的过程, 从而导致胞内一定区域的钙离子浓度降低, 最终激活低钙敏感的通道开放, 离子流动引发电位改变, 由此周而复始即形成了规律性的电位变化. 虽然目前关于胃肠道起搏机制的研究已取得一定进展, 但在这个领域中还有许多有争论的学说, 例如起搏通道究竟是氯通道还是非选择性阳离子通道的争论就一直存在, 另外ryanodine敏感的钙库以及胃肠道其他类型ICC是否也参与起搏过程等许多问题尚未明了, 这说明ICC还需要大量深入的研究.

2.1 非选择性阳离子通道 如前所述, ICC-MY和ICC-IM两种细胞与胃肠道平滑肌的自发性收缩活动都有关, 都能产生自发性的电活动, 但ICC-MY产生的起搏电位和ICC-IM产生的单位电位机制有所不同. Takeda发现参与ICC-MY起搏电位的电流可被$[Ca^{2+}]i$增加而阻断, 具有低钙敏感性, 根据反转电位和对Na^+具有通透性的特点, 鉴定这种电流是非选择性阳离子通道(non-selective cation channel, NSCC)开放产生的, 在过去的研究中, 多数学者的数据都支持这一结论[10-13]. ICC-IM产生的单位电位是一种基础电流, 并有瞬间自发性内向电流(spontaneous transient inward currents, STICs)叠加于其上, 有CaM依赖性, $[Ca^{2+}]i$增加对电流具有促进作用, 这种电流同样对Na^+通透, 反转电位接近0 mV, 并能被Ga^{3+}阻断, 因此鉴定这种高钙激活的电流也是非选择性阳离子通道. 因为调整氯离子平衡电位(ECl)对两种细胞产生的电流都没有影响, 所以排除了有氯离子参与起搏电位和单位电位的可能性. Takeda等[13]认为在不同种类的ICC中表达不同机制的非选择性阳离子通道是ICC在胃肠起搏活动中行使不同功能的基础.

有研究表明, 参与胃肠道ICC-MY起搏活动的非选择性阳离子通道是一类特殊的瞬间受体电位(transient receptor potential, TRP)通道, 这种通道的特殊之处在于存在多种门控机制, 在视、触、嗅、听等感觉产生的机制中具有重要作用[14]. TRP通道是一类六次跨膜的非选择性阳离子通道, 包括7个亚型, 在TRP家族中至少两类亚型与胃肠道ICC-MY起搏电流相关: TRPC4[15]和TRPM7[16], 在HEK293细胞上异源表达这两种通道都会产生一种类似于ICC起搏电流的内向电流, 说明起搏通道有可能属于TRP通道家族.

2.2 氯通道 Tokutomi等[17]于1995年发现从小鼠小肠分离出的ICC起搏电流的翻转电位接近氯离子的翻转电位, 而且氯通道的阻断剂SITS抑制起搏电流, 因此他们认为, 起搏电流的产生与氯离子有关, 随后的许多研究结果也支持这一结论[18-21]. Kito等通过组织原位记录方法发现ICC-MY产生的起搏电位包括两个时相, 分别由不同电流参与: 第一时相是电位的快速上升期, 由电压依赖的钙通道开放造成; 第二时相是平台期, 由钙激活氯通道开放所致[19,20]. 虽然在培养的ICC上已发现高电导性、内向整流性和容积敏感性等氯通道[17,18,22], 但对氯通道为起搏通道这一观点持有异议的学者认为, 在新鲜分离的c-kit阳性ICC上并未发现钙激活氯通道, 只发现存在NSCCs通道[13]; 另外, 氯通道阻断剂缺乏特异性[23,24], 不仅能够阻断氯通道也能够阻断非选择性阳离子通道[12,25], 因此他们认为氯通道阻断剂能够阻断起搏电流的依据不足以说明起搏通道就是氯通道[13]. 但最新研究发现, 在胃肠道间质肿瘤(gastrointestinal stromal tumors, GIST)中存在一种特异性的ANO1蛋白(anoctamin 1/TMEM16A), 即钙激活氯通道蛋白, 这种蛋白不

仅是胃肠道ICC的特异性标志蛋白, 也参与慢波的产生过程[26-28], 这一结果有力地支持了氯通道参与起搏活动的结论. 最近Parsons等[21]还发现ICC-MY存在一种由ATP和PKA激活的外向整流氯电流(PKA- and ATP-activated chloride channel, PACC), 这种氯通道产生一种尾电流, 只参与ICC-MY起搏活动的后除极化过程. 因此可以认为, 胃肠道起搏细胞存在有多种氯通道, 与其他种类的通道共同参与起搏活动的产生和调节.

2.3 其他离子通道 除了前面所讲的非选择性阳离子通道和氯通道, 已经证实在胃肠道ICC上还存在钠、钾和钙等通道, 这些通道也参与调节ICC起搏活动, 对胃肠道的自发性收缩功能具有一定的影响. 在新鲜分离的狗近端结肠[29]和豚鼠胃窦[30]分别发现了IKCa的存在, 这种电流有可能参与胃肠道自发性内向电流的再去极化调节过程. 在鼠类和狗的小肠以及结肠发现了T型钙通道的存在[31-33], Gibbons等[34]研究表明, T型α1H钙通道的阻断剂能够阻断小鼠小肠ICC起搏电位的上升支, 因此推测T型α1H钙通道参与小鼠小肠起搏电位的产生, 但T型α1H钙通道不参与人小肠ICC的起搏活动[35]. 钠通道一直被认为在心脏起搏中起到关键作用, 而只有在最近几年才在胃肠ICC中发现SCN5A编码的NaV1.5钠通道, 这种钠通道参与慢波上升支的形成, 具有机械敏感性, 当细胞膜受到牵拉时, 内向钠电流峰值的幅度增加[36], 因此可以看出虽然钠通道并不是起搏通道, 但在胃肠动力的调节中起到重要的作用.

2.4 钙库和线粒体 钙离子在胃肠ICC起搏活动中扮演极其重要的角色, 钙离子从钙库中释放是激活起搏活动的起始机制[37,38], 已明确IP3敏感的钙库是胃肠道ICC产生起搏活动的关键结构[9,10], 但ryanodine敏感的钙库在胃肠道起搏活动中的作用还有争议. 有学者发现ryanodine对胃肠道慢波的电活动没有影响, 因此认为ryanodine敏感的钙库不参与起搏过程[7,38,39], 但Aoyama等则发现ryanodine能完全阻断胃肠ICC钙振荡, 因此认为ryanodine与IP3敏感的钙库应该是共同参与引起ICC起搏电流的钙振荡[40], 而且Aoyama等和Liu等也进一步发现胃肠ICC上存在ryanodine3受体(RyR3), 并对起搏活动有调节作用, 这一数据为ryanodine敏感的钙库参与起搏过程提供了有力的支持[40,41].

3 胃肠起搏功能与运动障碍

早在1995年Huizinga等[42]学者就发现胃肠道ICC网络消失会导致慢波消失, 从此人们逐渐发现胃肠道多种疾病与ICC有关. 已有证据表明, ICC网络的受损、异常、缺失或增生都会导致胃肠道慢波异常, 从而引起动物[43]或人[44,45]胃肠动力障碍或疾病, 如糖尿病性胃肠动力失调[46]; 功能性消化不良[47]; 假性肠梗阻[48]; 贲门失弛缓症[49]; 幽门狭窄[49]等. 甚至一些肿瘤也与ICC有关, 如GIST是一种常见的胃肠道间质肉瘤, 特征性地过量表达由*c-kit*原癌基因编码的酪氨酸激酶受体CD117[50-52]. 因此, 与ICC相关疾病的研究日益得到重视.

关于胃肠动力疾病的治疗, 多数学者认为, ICC可以成为治疗的靶向目标[53,54]. 一些能够影响ICC功能的药物已应用于临床或正在研究当中. *c-kit*原癌基因的过度表达是导致GIST发生的主要原因, 一直以来因为其对放疗和化疗不为敏感, 手术治疗成为唯一的手段, 但治疗效果不佳. 自从2001年Joensuu等[55]首次报道酪氨酸激酶受体阻断剂imabinib应用于治疗GISTs以后, imabinib逐渐在临床得到应用, 并收到良好的治疗效果[50-52]. 目前与ICC有关的促胃动力药物的研究也有所进展. DA-9701是一种由牵牛种子和延胡索块茎合成的中草药型促运动剂, 可通过激活ICC的起搏活性加速胃排空速度, 增加胃顺应性, 其促进胃肠动力的效果强于莫沙必利和西沙必利[56,57], 目前在韩国已用于治疗功能性消化不良病的临床III期试验阶段[56]. 最新的治疗胃肠动力疾病的方法显示, 对于一些因ICC的缺失或功能异常所导致胃肠动力疾病, 可以采用骨髓移植的方法植入具有多种分化潜能的多能干细胞, 进而促使其转分化为ICC, 从而恢复胃肠动力[58]. 与ICC有关的临床用药及治疗方法为胃肠动力疾病的治疗开辟了新的方向.

4 结论

多数学者的研究结果已证实胃肠道的起搏活动与ICC的自发节律性电活动相关, 细胞内自发性钙震荡是引起ICC起搏活动的重要机制, 其中IP3介导的钙库对钙离子节律性的钙释放是关键环节; 多种胃肠道疾病, 尤其是动力障碍性疾病与ICC的损伤或缺失具有密切的关系. 然而, 关于胃肠平滑肌的起搏功能研究还有许多问题尚待解决, 如起搏电流的离子机制、疾病过程中引起ICC损伤并缺失的机制等. 总之, 为明确胃肠动力障碍性疾病的发病机制, 研究ICC起搏活动的产生机制以及其在胃肠疾病发生发展过程

■名词解释

TRP通道: 是一类六次跨膜的非选择性阳离子通道, 分为7大类: TRPC、TRPV、TRPM、TRPA、TRPN、TRPP和TRPML, 存在于不同种类的生物中, 包括蠕虫、植物、鱼类、鼠类和人类. TRP通道在可兴奋和非兴奋细胞中具有多种功能. 其中, TRP通道最重要的作用是具有感觉功能, 作为最古老的细胞感受装置, TRP通道不仅感受外界刺激, 如视觉、听觉、触觉、温度觉、味觉和嗅觉等, 同时也感受内环境的变化, 如酸碱度或激素水平的变化等.

■同行评价
本文系统阐述了平滑肌运动机制和起搏机制研究的历史及现状, 文献引用合理, 比较全面, 能够反映当前该领域的研究现状.

中所起的作用具有重要的临床意义.

5 参考文献

1 Ambache N. The electrical activity of isolated mammalian intestines. *J Physiol* 1947; 106: 139-153
2 Ward SM, Sanders KM. Interstitial cells of Cajal: primary targets of enteric motor innervation. *Anat Rec* 2001; 262: 125-135
3 Dickens EJ, Hirst GD, Tomita T. Identification of rhythmically active cells in guinea-pig stomach. *J Physiol* 1999; 514 (Pt 2): 515-531
4 Ordög T, Ward SM, Sanders KM. Interstitial cells of cajal generate electrical slow waves in the murine stomach. *J Physiol* 1999; 518 (Pt 1): 257-269
5 Edwards FR, Hirst GD, Suzuki H. Unitary nature of regenerative potentials recorded from circular smooth muscle of guinea-pig antrum. *J Physiol* 1999; 519 Pt 1: 235-250
6 Sanders KM. A case for interstitial cells of Cajal as pacemakers and mediators of neurotransmission in the gastrointestinal tract. *Gastroenterology* 1996; 111: 492-515
7 Malysz J, Donnelly G, Huizinga JD. Regulation of slow wave frequency by IP(3)-sensitive calcium release in the murine small intestine. *Am J Physiol Gastrointest Liver Physiol* 2001; 280: G439-G448
8 Sanders KM, Koh SD, Ward SM. Interstitial cells of cajal as pacemakers in the gastrointestinal tract. *Annu Rev Physiol* 2006; 68: 307-343
9 Suzuki H, Takano H, Yamamoto Y, Komuro T, Saito M, Kato K, Mikoshiba K. Properties of gastric smooth muscles obtained from mice which lack inositol trisphosphate receptor. *J Physiol* 2000; 525 Pt 1: 105-111
10 Ward SM, Ordog T, Koh SD, Baker SA, Jun JY, Amberg G, Monaghan K, Sanders KM. Pacemaking in interstitial cells of Cajal depends upon calcium handling by endoplasmic reticulum and mitochondria. *J Physiol* 2000; 525 Pt 2: 355-361
11 Goto K, Matsuoka S, Noma A. Two types of spontaneous depolarizations in the interstitial cells freshly prepared from the murine small intestine. *J Physiol* 2004; 559: 411-422
12 Koh SD, Jun JY, Kim TW, Sanders KM. A Ca(2+)-inhibited non-selective cation conductance contributes to pacemaker currents in mouse interstitial cell of Cajal. *J Physiol* 2002; 540: 803-814
13 Takeda Y, Koh SD, Sanders KM, Ward SM. Differential expression of ionic conductances in interstitial cells of Cajal in the murine gastric antrum. *J Physiol* 2008; 586: 859-873
14 Venkatachalam K, Montell C. TRP channels. *Annu Rev Biochem* 2007; 76: 387-417
15 Walker RL, Koh SD, Sergeant GP, Sanders KM, Horowitz B. TRPC4 currents have properties similar to the pacemaker current in interstitial cells of Cajal. *Am J Physiol Cell Physiol* 2002; 283: C1637-C1645
16 Kim BJ, Lim HH, Yang DK, Jun JY, Chang IY, Park CS, So I, Stanfield PR, Kim KW. Melastatin-type transient receptor potential channel 7 is required for intestinal pacemaking activity. *Gastroenterology* 2005; 129: 1504-1517
17 Tokutomi N, Maeda H, Tokutomi Y, Sato D, Sugita M, Nishikawa S, Nishikawa S, Nakao J, Imamura T, Nishi K. Rhythmic Cl- current and physiological roles of the intestinal c-kit-positive cells. *Pflugers Arch* 1995; 431: 169-177
18 Huizinga JD, Zhu Y, Ye J, Molleman A. High-conductance chloride channels generate pacemaker currents in interstitial cells of Cajal. *Gastroenterology* 2002; 123: 1627-1636
19 Kito Y, Fukuta H, Suzuki H. Components of pacemaker potentials recorded from the guinea pig stomach antrum. *Pflugers Arch* 2002; 445: 202-217
20 Kito Y, Suzuki H. Properties of pacemaker potentials recorded from myenteric interstitial cells of Cajal distributed in the mouse small intestine. *J Physiol* 2003; 553: 803-818
21 Parsons SP, Sanders KM. An outwardly rectifying and deactivating chloride channel expressed by interstitial cells of cajal from the murine small intestine. *J Membr Biol* 2008; 221: 123-132
22 Zhu Y, Mucci A, Huizinga JD. Inwardly rectifying chloride channel activity in intestinal pacemaker cells. *Am J Physiol Gastrointest Liver Physiol* 2005; 288: G809-G821
23 Dick GM, Kong ID, Sanders KM. Effects of anion channel antagonists in canine colonic myocytes: comparative pharmacology of Cl-, Ca2+ and K+ currents. *Br J Pharmacol* 1999; 127: 1819-1831
24 Welsh DG, Nelson MT, Eckman DM, Brayden JE. Swelling-activated cation channels mediate depolarization of rat cerebrovascular smooth muscle by hyposmolarity and intravascular pressure. *J Physiol* 2000; 527 Pt 1: 139-148
25 Koh SD, Sanders KM, Ward SM. Spontaneous electrical rhythmicity in cultured interstitial cells of cajal from the murine small intestine. *J Physiol* 1998; 513 (Pt 1): 203-213
26 Gomez-Pinilla PJ, Gibbons SJ, Bardsley MR, Lorincz A, Pozo MJ, Pasricha PJ, Van de Rijn M, West RB, Sarr MG, Kendrick ML, Cima RR, Dozois EJ, Larson DW, Ordog T, Farrugia G. Ano1 is a selective marker of interstitial cells of Cajal in the human and mouse gastrointestinal tract. *Am J Physiol Gastrointest Liver Physiol* 2009; 296: G1370-G1381
27 Hwang SJ, Blair PJ, Britton FC, O'Driscoll KE, Hennig G, Bayguinov YR, Rock JR, Harfe BD, Sanders KM, Ward SM. Expression of anoctamin 1/TMEM16A by interstitial cells of Cajal is fundamental for slow wave activity in gastrointestinal muscles. *J Physiol* 2009; 587: 4887-4904
28 Zhu MH, Kim TW, Ro S, Yan W, Ward SM, Koh SD, Sanders KM. A Ca(2+)-activated Cl(-) conductance in interstitial cells of Cajal linked to slow wave currents and pacemaker activity. *J Physiol* 2009; 587: 4905-4918
29 Langton P, Ward SM, Carl A, Norell MA, Sanders KM. Spontaneous electrical activity of interstitial cells of Cajal isolated from canine proximal colon. *Proc Natl Acad Sci U S A* 1989; 86: 7280-7284
30 Kim YC, Suzuki H, Xu WX, Choi W, Kim SH, Lee SJ. Ca2+-activated K+ current in freshly isolated c-Kit positive cells in guinea-pig stomach. *J Korean Med Sci* 2009; 24: 384-391
31 Kim YC, Koh SD, Sanders KM. Voltage-dependent inward currents of interstitial cells of Cajal from murine colon and small intestine. *J Physiol* 2002; 541: 797-810
32 Koh SD, Monaghan K, Ro S, Mason HS, Kenyon JL, Sanders KM. Novel voltage-dependent non-selective cation conductance in murine colonic

myocytes. *J Physiol* 2001; 533: 341-355
33 Lee HK, Sanders KM. Comparison of ionic currents from interstitial cells and smooth muscle cells of canine colon. *J Physiol* 1993; 460: 135-152
34 Gibbons SJ, Strege PR, Lei S, Roeder JL, Mazzone A, Ou Y, Rich A, Farrugia G. The alpha1H Ca2+ Channel Subunit is Expressed in Mouse Jejunal Interstitial Cells of Cajal and Myocytes. *J Cell Mol Med* 2008 Dec 24. *[Epub ahead of print]*
35 Farrugia G. Ca2+ handling in human interstitial cells of Cajal. *Gastroenterology* 2007; 132: 2057-2059
36 Strege PR, Ou Y, Sha L, Rich A, Gibbons SJ, Szurszewski JH, Sarr MG, Farrugia G. Sodium current in human intestinal interstitial cells of Cajal. *Am J Physiol Gastrointest Liver Physiol* 2003; 285: G1111-G1121
37 Nose K, Suzuki H, Kannan H. Voltage dependency of the frequency of slow waves in antrum smooth muscle of the guinea-pig stomach. *Jpn J Physiol* 2000; 50: 625-633
38 van Helden DF, Imtiaz MS, Nurgaliyeva K, von der Weid P, Dosen PJ. Role of calcium stores and membrane voltage in the generation of slow wave action potentials in guinea-pig gastric pylorus. *J Physiol* 2000; 524 Pt 1: 245-265
39 Ward SM, Baker SA, de Faoite A, Sanders KM. Propagation of slow waves requires IP3 receptors and mitochondrial Ca2+ uptake in canine colonic muscles. *J Physiol* 2003; 549: 207-218
40 Aoyama M, Yamada A, Wang J, Ohya S, Furuzono S, Goto T, Hotta S, Ito Y, Matsubara T, Shimokata K, Chen SR, Imaizumi Y, Nakayama S. Requirement of ryanodine receptors for pacemaker Ca2+ activity in ICC and HEK293 cells. *J Cell Sci* 2004; 117: 2813-2825
41 Liu HN, Ohya S, Wang J, Imaizumi Y, Nakayama S. Involvement of ryanodine receptors in pacemaker Ca2+ oscillation in murine gastric ICC. *Biochem Biophys Res Commun* 2005; 328: 640-646
42 Huizinga JD, Thuneberg L, Klüppel M, Malysz J, Mikkelsen HB, Bernstein A. W/kit gene required for interstitial cells of Cajal and for intestinal pacemaker activity. *Nature* 1995; 373: 347-349
43 Sanders KM, Ordög T, Ward SM. Physiology and pathophysiology of the interstitial cells of Cajal: from bench to bedside. IV. Genetic and animal models of GI motility disorders caused by loss of interstitial cells of Cajal. *Am J Physiol Gastrointest Liver Physiol* 2002; 282: G747-G756
44 Geraldino RS, Ferreira AJ, Lima MA, Cabrine-Santos M, Lages-Silva E, Ramirez LE. Interstitial cells of Cajal in patients with chagasic megacolon originating from a region of old endemicity. *Pathophysiology* 2006; 13: 71-74
45 Pardi DS, Miller SM, Miller DL, Burgart LJ, Szurszewski JH, Lennon VA, Farrugia G. Paraneoplastic dysmotility: loss of interstitial cells of Cajal. *Am J Gastroenterol* 2002; 97: 1828-1833
46 Yamamoto T, Watabe K, Nakahara M, Ogiyama H, Kiyohara T, Tsutsui S, Tamura S, Shinomura Y, Hayashi N. Disturbed gastrointestinal motility and decreased interstitial cells of Cajal in diabetic db/db mice. *J Gastroenterol Hepatol* 2008; 23: 660-667
47 Zhang H, Xu X, Wang Z, Li C, Ke M. Correlation between gastric myoelectrical activity recorded by multi-channel electrogastrography and gastric emptying in patients with functional dyspepsia. *Scand J Gastroenterol* 2006; 41: 797-804
48 Isozaki K, Hirota S, Miyagawa J, Taniguchi M, Shinomura Y, Matsuzawa Y. Deficiency of c-kit+ cells in patients with a myopathic form of chronic idiopathic intestinal pseudo-obstruction. *Am J Gastroenterol* 1997; 92: 332-334
49 Vanderwinden JM, Rumessen JJ. Interstitial cells of Cajal in human gut and gastrointestinal disease. *Microsc Res Tech* 1999; 47: 344-360
50 Annaberdyev S, Gibbons J, Hardacre JM. Dramatic response of a gastrointestinal stromal tumor to neadjuvant imatinib therapy. *World J Surg Oncol* 2009; 7: 30
51 Dagher R, Cohen M, Williams G, Rothmann M, Gobburu J, Robbie G, Rahman A, Chen G, Staten A, Griebel D, Pazdur R. Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. *Clin Cancer Res* 2002; 8: 3034-3038
52 Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corless C, Fletcher CD, Joensuu H. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002; 347: 472-480
53 Farrugia G. Interstitial cells of Cajal in health and disease. *Neurogastroenterol Motil* 2008; 20 Suppl 1: 54-63
54 Huizinga JD, Thuneberg L, Vanderwinden JM, Rumessen JJ. Interstitial cells of Cajal as targets for pharmacological intervention in gastrointestinal motor disorders. *Trends Pharmacol Sci* 1997; 18: 393-403
55 Joensuu H, Roberts PJ, Sarlomo-Rikala M, Andersson LC, Tervahartiala P, Tuveson D, Silberman S, Capdeville R, Dimitrijevic S, Druker B, Demetri GD. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001; 344: 1052-1056
56 Choi S, Choi JJ, Jun JY, Koh JW, Kim SH, Kim DH, Pyo MY, Choi S, Son JP, Lee I, Son M, Jin M. Induction of pacemaker currents by DA-9701, a prokinetic agent, in interstitial cells of Cajal from murine small intestine. *Mol Cells* 2009; 27: 307-312
57 Lee TH, Choi JJ, Kim DH, Choi S, Lee KR, Son M, Jin M. Gastroprokinetic effects of DA-9701, a new prokinetic agent formulated with Pharbitis Semen and Corydalis Tuber. *Phytomedicine* 2008; 15: 836-843
58 Ishii S, Tsuji S, Tsujii M, Nishida T, Watabe K, Iijima H, Takehara T, Kawano S, Hayashi N. Restoration of gut motility in Kit-deficient mice by bone marrow transplantation. *J Gastroenterol* 2009; 44: 834-841

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