· 综述 ·

神经调节蛋白 1 在髓鞘生成中的相关调控因子研究进展

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【摘要】 髓鞘是包裹在神经轴突外面的一层髓磷脂膜，对于神经电信号的快速传导有着重要作用。自轴突和细胞外基质的信号参与髓鞘的生成并发挥关键性作用。研究表明，神经轴突及施万细胞可分泌神经调节蛋白 1（NRG1），且 NRG1 对于施万细胞的分化、增殖、迁移及髓鞘形成、修复存在重要作用。但 NRG1 与其他参与髓鞘形成的信号蛋白（层黏连蛋白 -211、Maf、Gab1、E- 钙黏蛋白）的相互调控尚不完全清楚。现主要对此作一综述，以进一步诠释髓鞘生成中的分子机制。

【关键词】 神经调节蛋白 1； 髓鞘生成； 调控； 信号蛋白； 综述

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【**Abstract**】 The myelin sheath is a layer of myelin membrane that is wrapped around the axons. It plays an important role in the rapid conduction of nerve electrical signals. The production of myelin is a complex dynamic process in which signals from axons and extracellular matrices participate and play a key role. Neuregulin 1 (NRG1) is a group of trophic factors. Studies have shown that axons and Schwann cells can secrete NRG1, and NRG1 plays an important role in the differentiation, proliferation, migration and myelination and repair of Schwann cells. However, the regulation of NRG1 with other signaling proteins involved in myelination (laminin-211, Maf, Gab1, E-cadherin) is not fully understood. This article is mainly to review this to further explain the molecular mechanism of myelination.

【**Key words**】 Neuregulin 1; Myelin production; Regulatory; Signal protein; Review

一、NRG1分类

神经调节蛋白1(neuregulin-1, NRG1)是含有表皮样生长因子(epidermal growth factor, EGF)活性结构域的一组生长因子,通过与酪氨酸激酶受体(ErbB)结合发挥作用。目前已经描述了至少31种人源性NRG1。NRG1包含单个跨膜结构域和N-末端的免疫球蛋白样结构域。根据N-末端结构域不同,NRG1分为Ⅰ~Ⅵ型。目前Ⅰ~Ⅳ型NRG1研究较多,较少有人对Ⅴ~Ⅵ型进行描述[1-2]。NRG1可分为可溶性(Ⅰ型、Ⅱ型)和跨膜性(Ⅲ型)。NRG1 Ⅰ型和Ⅱ型可直接分泌,也可在蛋白水解后作为可溶性蛋白从细胞表面释放,具有独特的扩散和黏附富含硫酸乙酰肝素的细胞表面的能力;Ⅲ型含有富含半胱氨酸的结构域,需要蛋白水解以获得完全活性并以juxtacrine方式发出信号。Ⅰ型和Ⅱ型NRG1与附近细胞表面上表达的ErbB受体进行旁分泌信号传导,并作为可扩散信号释放。Ⅲ型NRG1只能与位于相邻细胞上的受体进行邻分泌信号传导;邻分泌相互作用可以正性和负性调控信号,信号进一步转移到细胞核并影响基因转录。根据靠近EGF样结构域的小结构域不同,NRG1同种型可以进一步分为α和β同种型;或者根据包含在C末端的外显子分为a、b和c同种型[3-6]。

二、NRG1在髓鞘形成中的相关调控因子

NRG1通过与施万细胞中ErbB2/3异二聚体结合发生生物信号传递。NRG1与受体结合后,ErbB2/3异二聚体的酪氨酸激酶被激活并诱导各种信号通路,包括PI3K-Akt、ERK1/2、FAK、Rac1和cdc42,以及钙调神经磷酸酶信号通路的激活,并将信号传递给下游信号分子,进而参与神经元发育、迁移、轴突生长和突触功能[7]。

1.层黏连蛋白-211(Lm211):层黏连蛋白是由1条α、1条β和1条γ链组成的三聚体糖蛋白[8],按结构可分为十字形(3个短臂和1个长卷曲螺旋臂,例如Lm111、Lm211、Lm511)、Y形(无α-短臂,例如:Lm411)或杆状(截短的短臂,Lm3A32)。Lm211主要存在于周围神经施万细胞和骨骼肌基底膜,其由α2、β1和γ1链组成,分别由lama2、lamb1和lamc1基因编码[9]。

施万细胞在周围神经中形成髓鞘有2个步骤:轴突的径向排序和髓鞘化。在径向排序过程中,未成熟的施万细胞将直径大于1 μm的轴突分离到未成熟轴突束边缘,然后与这些轴突形成1∶1的关系[10]。通过cAMP和蛋白激酶A(PKA)组成的信号通路激活Egr2后,施万细胞开始在轴突周围形成髓鞘。这些发育步骤由NRG1 Ⅲ和Lm211调节。

将外源性Lm211添加到大鼠背根神经节细胞培养基中,施万细胞使神经元髓鞘化,反之则不存在髓鞘化;但在无NRG1 Ⅲ的情况下,Lm211不能诱导髓鞘形成,提示Lm211的髓鞘形成作用依赖于NRG1 Ⅲ。Nrg1 Ⅲ$^{+/-}$小鼠的坐骨神经表现出较薄的髓鞘,lama2$^{-/-}$小鼠的坐骨神经髓鞘厚度没有显著变化,但Nrg1 Ⅲ$^{+/-}$/lama2$^{-/-}$小鼠的神经显示髓鞘厚度恢复接近野生型水平,表明Lm211的缺失改善了Nrg1 Ⅲ$^{+/-}$导致的髓鞘变薄。而在NRG1 Ⅲ TG(NRG1 Ⅲ过表达)/lama2$^{-/-}$小鼠神经中观察到,远小于1 μm的无髓鞘轴突被厚髓鞘包围。证明Lm211具有抑制NRG1 Ⅲ在小口径轴突生成髓鞘的作用。已知PKA可被NRG1激活,且PKA可独立于NRG1激活ErbB2-Gab1轴及下游的oct6和egr2。在NRG1 Ⅲ TG/lama2$^{-/-}$小鼠中,敲除Lm211显著增加ErbB2和Gab1的磷酸化,而在NRG1 Ⅲ TG的神经中,ErbB2和Gab1的磷酸化没有增加;给予PKA抑

制剂显著降低了NRG1 Ⅲ TG/lama2^{-}小鼠的ErbB2及Gab1的激活。这些结果表明Lm211限制通过PKA的NRG1 Ⅲ信号传导，从而防止施万细胞过早分化、抑制小于1 μm的纤维髓鞘形成，调控小纤维中的髓鞘厚度[11]。

2.转录因子Maf：Maf是bZIP转录因子MAF家族的成员，其激活或抑制靶基因。MAF家族有两个不同的亚群，根据分子大小可分为：小Maf转录因子（150～160个氨基酸：MAFF、MAMG和MAFK）和大Maf转录因子（240～340个氨基酸：MAFA、MAFB、C-MAF和NRL）。小Maf蛋白缺乏具有激活功能的组氨酸/甘氨酸重复区和富含P/S/T的酸性结构域，其存在于大的Maf蛋白中。Maf涉及多种发育过程并控制晶状体、胰腺、软骨、造血细胞和感觉神经元的分化[12]。

髓鞘的主要成分为髓磷脂，由施万细胞产生。髓磷脂中最丰富的脂质成分是胆固醇。但施万细胞形成髓鞘所需的胆固醇不能血液循环中获得，依赖于自身合成[13]。已知施万细胞开始形成髓鞘时，Maf也开始表达。在Maf和ErbB2消融小鼠的神经中均观察到胆固醇水平的显著降低，提示Maf和NRG1在施万细胞胆固醇合成中均起到关键作用。进一步研究发现NRG1-ErbB信号调节Maf：重组NRG1促进S16细胞以时间依赖性方式诱导Maf mRNA，而ErbB2消融小鼠神经中Maf mRNA较健康对照组减少了50%～60%。当给予两种不同的Ca^{2+}信号通路抑制剂［plcγ的抑制剂、ip3受体(ip3r)的拮抗剂］后，阻断了依赖NRG1的Maf转录，表明Maf转录依赖于Nrg1下游的钙调蛋白依赖性激酶。研究结果表明，NRG1-ErbB信号通路调控Maf的表达[14]。

3. Gab1：Grb2相关结合物(Grb2-associated binding protein 2，GABs)是通过受体酪氨酸激酶参与细胞信号传导的支架蛋白。GABs家族包括Gab1、Gab2和Gab3。Gab1与多种信号分子相互作用，如蛋白酪氨酸磷酸酶2(Shp2)、PI3K调节亚单位P85、磷脂酶C-γ和Grb2。Gab1对于胚胎、心脏、皮肤及肌肉的发育存在决定性作用[15]。Gab2的作用与Gab1的作用相似，而Gab3无明显功能[16]。GABs为含SH2结构域的信号蛋白提供了停靠位点，如Shp2和p85，进而分别激活ERK和Akt[17]。已知NRG1通过激活PI3K/Akt和ERK进行信号传导。从施万细胞中去除Gab1后导致了髓鞘发育不良和Remak束的发育异常；而在Gab2敲除小鼠中未观察到这些异常。在髓鞘形成期间，坐骨神经中Gab1而非Gab2的酪氨酸磷酸化被上调，并且在NRG1 Ⅲ$^{+/-}$小鼠中Gab1受到抑制，其表现出类似于Gab1敲除小鼠的髓鞘减少表型。Gab1敲除和NRG1 Ⅲ$^{+/-}$小鼠的髓鞘神经细胞外信号调节激酶活性均降低。这些提示Gab1参与了周围神经发育过程中NRG1信号通路传导[18]。

4. E-钙黏蛋白：E-钙黏蛋白是经典钙黏蛋白家族的成员。钙黏蛋白在胚胎发育和成体组织内稳态中起着重要作用。E-钙黏蛋白是黏附连接的组成部分，介导钙依赖性细胞黏附和细胞连接形成，对调节细胞接触起重要作用。在细胞质中，E-钙黏蛋白与α、β和p120连环蛋白结合，激活Hippo、Wnt、TGFβ、NF-κB和其他生长因子信号通路，起到生长发育的作用。E-钙黏蛋白同种结合也可通过调节生长抑制信号［包括Hipp、o途径生长因子受体酪氨酸激酶(RTK)和SRC家族激酶信号途径］发挥接触介导的生长抑制。已有研究显示E-钙黏蛋白是胚胎干细胞自我更新过程中的重要分子，对维持造血干细胞的干性及胰腺外分泌部结构的完整性也很重要。近些年E-钙黏蛋白也被证实可以抑制癌细胞增殖[19-21]。

在周围神经中，E-钙黏蛋白表达定位于施万细胞并且在组织发生时出现。在成熟髓鞘中，E-钙黏蛋白存在于黏附连接中，介导非紧密髓鞘区域内的自体膜接触，稳定非致密髓鞘区域的结构[22-24]。在动物模型中，施万细胞中特异性E-钙黏蛋白消融导致早期髓鞘形成延迟。同样在施万细胞与背根神经节神经元共培养中，E-钙黏蛋白缺失减弱髓鞘形成、缩短髓鞘段长度。在施万细胞中，E-钙黏蛋白过度表达可改善NRG1 Ⅲ$^{+/-}$神经元的髓鞘形成，并诱导交感神经正常无髓鞘轴突的髓鞘形成。E-钙黏蛋白的促髓鞘形成作用与增强的NRG1-ErbB受体信号相关，包括激活下游Akt和Rac。在缺乏E-钙黏蛋白的情况下，施万细胞中的NRG1信号减弱，轴突NRG1 Ⅲ型可诱导施万细胞中的E-钙黏蛋白表达，这表明E-钙黏蛋白与NRG1信号相互作用。总之，E-钙黏蛋白具有促进施万细胞髓鞘形成和调节NRG1信号的功能[25]。

综上，在周围神经系统中，NRG1发挥着促进施万细胞分化、增殖、迁移及髓鞘形成的作用。随着NGR1的功能及与其他分子调控机制的阐明，为解释某些周围神经病的发生发展及治疗提供了潜在的理论依据。

利益冲突 文章所有作者共同认可文章无相关利益冲突

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