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淋巴管系统相关研究现状与展望

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摘要 近20年来, 淋巴管研究取得了长足的进展. 淋巴管系统在维持组织体液平衡、免疫监控, 以及脂质吸收转运等生理过程中起重要作用. 淋巴管发育缺陷或由于感染、创伤等引起淋巴液回流障碍可导致淋巴水肿; 淋巴管异常生长也参与许多重大疾病的发生与发展, 包括肿瘤转移、炎症、心血管疾病等. 深入了解淋巴管在生理与病理过程中的功能调控机制, 对于人类健康及相关疾病的防治具有重要的意义.

关键词 淋巴管生成, 体液平衡, 免疫监控, 脂质代谢, 淋巴水肿, 肿瘤转移

脊椎动物的淋巴管网络是一个相对独立的单向运输系统, 与血管循环系统在发育与功能上密切相关. 除骨髓、神经等少数组织外, 淋巴管几乎遍布全身, 在维持组织体液平衡、免疫监控, 以及脂质吸收转运等生理过程中起重要作用; 淋巴管异常生长也参与许多重大疾病的发生与发展. 近年来, 陆续发现了淋巴管特异性标记物、淋巴管分化与生长调控因子, 以及淋巴管内皮细胞外基质蛋白与细胞内信号传导因子, 对淋巴管系统的认识取得了较大的进步, 由此开拓了脉管循环系统研究的一个新领域——淋巴管生物医学[1~3].

1 淋巴管发育

1.1 淋巴管起源

哺乳类动物的淋巴管主要源于静脉, 在胚胎发育过程中先形成淋巴囊状结构, 并经发芽式生长与成熟重塑等过程形成淋巴管网络系统; 而在鸟类等动物, 淋巴管发生有双重来源, 包括静脉内皮细胞与间充质细胞[4~6]. 近来研究发现, 小鼠(*Mus musculus*)心脏与皮肤等组织中存在非静脉内皮来源的淋巴管生成[7~9]. 淋巴管内皮细胞的分化过程受多因子协同调控, 包括关键转录因子PROX1, SOX18以及COUP-TFⅡ. 在小鼠敲除*Prox1*基因可阻断静脉内皮细胞分化成淋巴管内皮细胞[10]. PROX1的表达受SOX18与COUP-TFⅡ的调节, SOX18失活突变(Ragged突变体)与*Sox18*基因敲除或小鼠胚胎发育早期缺失COUP-TFⅡ都可导致淋巴管内皮细胞分化障碍[11~13]. 此外, 视黄酸与NOTCH1可参与淋巴管分化调控, 在敲除编码视黄酸降解酶基因*Cyp26b1*的突变体小鼠, 淋巴管内皮祖细胞在主静脉与淋巴囊异常增加[14]. 缺失*Notch1*也可导致淋巴管内皮祖细胞增加, 而激活NOTCH1信号途径则抑制淋巴管内皮细胞分化[15].

淋巴管内皮细胞分化形成原始淋巴囊结构后必须与血管分离. 目前对于调控淋巴管与血管分离的信号途径已有深入了解, 源于巨核细胞的血小板在

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此过程中发挥重要作用[16~18]. 利用*Meis1*基因敲除小鼠的研究发现, 该突变小鼠缺少巨核细胞从而导致淋巴管与血管之间发生异常汇合[19]. 进一步研究表明, 淋巴管表达的平足蛋白(podoplanin, PDPN)与血小板CLEC2是调节淋巴管-血管分离的重要信号途径, 在*Clec2*或*Pdpn*基因敲除小鼠, 血管和淋巴管存在非正常连接. 另外, 小鼠缺失平足蛋白O-糖基化所需要的T-合成酶(*C1galt1*基因敲除)也发生与*Pdpn*基因敲除小鼠类似的表型[20]. SYK, SLP76与PLCγ2是PDPN-CLEC2信号通路的下游因子, 敲除上述基因同样导致小鼠淋巴管-血管分离缺陷, 从而发生胚胎期致死[21,22]. 淋巴与血液循环相对独立性的建立, 对于维持脉管循环系统的结构与功能至关重要.

1.2 淋巴管新生

淋巴管新生, 即其通过发芽式生长形成淋巴管网络系统的过程. 受体酪氨酸激酶血管内皮细胞生长因子受体-3(vascular endothelial growth factor receptor 3, VEGFR-3)介导的信号途径在调节淋巴管新生过程中极为关键. VEGFR-3在小鼠胚胎发育早期的血管内皮细胞有表达, 但从妊娠中期后主要表达在淋巴管内皮细胞. 已知的VEGFR-3配体有VEGF-C及VEGF-D, 其在血管内皮与间充质细胞等多种细胞中均有表达[23~26]. *Vegfc*基因敲除小鼠导致淋巴管发育缺陷及胚胎期致死[23], 但敲除*Vegfd*基因不影响淋巴管发育[27]. 敲除*Vegfr3*基因导致小鼠胚胎在淋巴管发生前死亡, 主要表型为胚胎与卵黄囊的血管发育受阻[24]. 利用靶向VEGFR-3配体结合区的条件性基因敲除小鼠的研究证实, 配体介导的VEGFR-3激活在淋巴管生长中起重要作用, 但VEGFR-3在血管发育中的作用可能是负向调控VEGFR-2介导的信号途径[25]. 另外, VEGFR-3信号途径受多种因子的调节. 敲除VEGFR-3共受体NRP2导致小鼠毛细淋巴管及前集合淋巴管显著减少, 而大集合淋巴管发育不受影响[26]. CCBE1通过促进ADAMTS3介导的VEGF-C成熟从而参与淋巴管的生长调节[28], 小鼠缺失ADAMTS3同样导致淋巴管发育异常[29]. 可溶性VEGFR-2(sVEGFR-2)通过抑制VEGF-C从而阻断VEGFR-3介导的信号途径[30]. SPREAD-1和SPREAD-2可抑制VEGFR-3介导的ERK信号通路[31]. RASA1通过抑制由VEGFR-3诱导的Ras信号途径, 对淋巴管内皮细胞的增殖起负调节作用[32]. TGF-β也负向调节VEGFR-3信号通路[33]. EphrinB2控制VEGFR-3的内吞及其下游信号通路[34]. DLL4和NOTCH-1通过调节EphrinB2表达和VFGFR-3介导的信号参与淋巴管发育调控[35], 且DLL4在肠绒毛淋巴管再生过程中起重要作用[36]. 因此, 淋巴管网络形成是一个多因子/信号途径协同调节的复杂过程.

1.3 淋巴管网络成熟重塑

原始淋巴囊经淋巴管新生形成初级网络后, 还需进一步重塑才能发育为成熟的淋巴管网络系统. 淋巴管成熟重塑过程包括集合淋巴管管腔形成、管壁平滑肌细胞招募, 以及管腔内瓣膜发育. FOXC2和NFATc1通过抑制ANGPT2和PDGF-B的表达参与调节淋巴管平滑肌细胞的招募, 在小鼠敲除*Foxc2*基因导致淋巴管异常招募平滑肌细胞[37~39]. 在缺少Ephrin-B2C-末端PDZ结合位点的基因突变体小鼠, 可发生毛细淋巴管异常招募平滑肌细胞. 抑制SEMA3A/NRP-1信号途径也同样能增加淋巴管外周细胞的覆盖率[40], 而小鼠敲除胞外基质蛋白Reelin导致集合淋巴管形成异常与平滑肌细胞减少[41].

淋巴管成熟重塑过程也伴有腔内瓣膜的发生. 淋巴管瓣膜呈半月形结构, 瓣膜小叶以细胞外基质为核心, 两侧覆盖有淋巴管内皮细胞. 利用遗传修饰小鼠模型研究表明, 敲除*Foxc2*或下游靶基因*Cx37*导致小鼠淋巴管瓣膜发育异常[42,43]. GATA2是一种锌指转录因子, 通过调节 PROX1, FOXC2和NFATc1的表达, 参与淋巴管瓣膜发育调控[44~46]. 小鼠敲除*Angpt2*或*Tie1*基因阻断集合淋巴管生成与瓣膜发育[47~50]. SEMA3A/NRP-1介导的信号缺失也影响瓣膜发育[40,51]. 另外, TGFβ/BMP信号途径包括BMP9与ALK1也参与淋巴管网络与成熟调控[52,53]. 值得指出的是, 上述基因敲除小鼠模型常常同时发生集合淋巴管生成、平滑肌细胞招募及瓣膜发育的缺陷, 其中哪些表型是原发性的, 尚待深入剖析. 此外, 对于上述因子如何协同调控淋巴管成熟重塑尚了解很少.

2 淋巴管的生理作用机制

2.1 淋巴管与体液平衡

淋巴管在结构上不同于血管. 毛细淋巴管位于组织间隙内, 以膨大的盲端起始, 管壁由内皮细胞构成, 内皮细胞间重叠形成“钮扣样”连接, 管壁外有不

连续基底膜, 无外周细胞, 这些结构特征有助毛细淋巴管吸收液体、运输大分子物质以及免疫细胞. 集合淋巴管细胞间形成“拉链样”连接, 管腔内有瓣膜, 管壁有平滑肌细胞, 以助于淋巴液回流. 淋巴管内皮细胞通过特定的“锚丝”附着于管壁周围的胞外基质, 以保证淋巴管在组织液压增加时仍能保持开放状态[54,55]. 血液流经组织中的毛细血管网络时, 血浆中的液体及营养物质从动脉端毛细血管渗出进入组织间隙形成组织液, 与细胞之间进行物质交换, 部分组织液随后在静脉端毛细血管被重吸收入血液, 剩余部分的液体包括大分子物质与细胞通过毛细淋巴管吸收成为淋巴液. 淋巴液经淋巴结过滤, 最终经胸导管或右淋巴导管汇入静脉血液[56]. 淋巴液回流的内在动力取决于淋巴管平滑肌细胞阶段性和紧张性收缩, 从而驱动淋巴液的流动. 外部动力主要依赖周围组织的收缩和扩张, 包括心脏与血管动脉收缩、胃肠肌肉与骨骼肌收缩, 以及呼吸运动等. 淋巴管收缩泵功能对机械负荷的变化非常敏感, 受淋巴液体剪切力的直接影响, 淋巴管内皮细胞可通过释放一氧化氮来调控内在淋巴管的泵送功能[57]. 因此, 淋巴管通过主动参与组织液的吸收与转运, 在维持机体的体液平衡过程中起重要作用.

2.2 淋巴管与脂质吸收

肠绒毛中除丰富的血管网外, 还有中央淋巴管(又称乳糜管). 肠道内由饮食与肠道微生物等来源的物质包括氨基酸与单糖等主要通过肠绒毛内的毛细血管吸收, 而饮食脂质及脂溶性维生素等由肠黏膜上皮细胞吸收并被包装成乳糜微粒释放入组织间隙, 与其他运输脂质的载体分子结合后经初始淋巴管内皮细胞间的“扭扣样”连接处进入肠绒毛淋巴管. 另有研究发现, 脂质也可进行跨淋巴管内皮细胞(即细胞内)的转运. 淋巴液因含有大量脂溶性物质呈“乳白色”, 依赖于肠绒毛淋巴管周围的平滑肌细胞收缩而转运, 并通过肠系膜的集合淋巴管汇入淋巴循环系统[58~63].

小鼠肠道淋巴管在出生后发育形成. 利用淋巴管发育缺陷小鼠模型包括*Vegfr3*基因敲除或其激酶域失活性点突变小鼠[25,64]、*Prox1*基因敲除杂合子小鼠[65], 以及对临床病人进行的研究表明, 淋巴管结构与功能异常可导致乳糜微粒等脂蛋白渗出进入腹腔及胸腔, 形成乳糜性腹水、乳糜胸或局部性组织水肿等, 并伴有水肿部位脂肪组织的累积. 从淋巴管渗漏出来的淋巴液, 可能有促进脂肪细胞分化或脂质沉积的作用. 研究发现, *Prox1*基因敲除杂合子小鼠还发生肥胖, 且小鼠肥胖发生程度与淋巴管结构异常及淋巴液渗漏程度相关[65]. 但肥胖现象在其他有淋巴管异常的小鼠模型中没有发生, 包括上述*Vegfr3*突变体小鼠[3]. 由于PROX1在肝脏及骨胳肌等组织中有表达, *Prox1*突变体小鼠肥胖可能与PROX1参与代谢调控有关. 进一步研究发现, 在成年小鼠诱导敲除*Vegfc*可引起肠绒毛淋巴管退化, 导致脂质吸收减少, 并抑制高脂饮食诱导的肥胖[66]. 因此, 有关淋巴管参与脂质代谢及其在肥胖发生中的作用机制有待于深入研究.

2.3 淋巴管与免疫监控

淋巴管系统通过运输免疫细胞及可溶性抗原参与免疫监控[2]. 淋巴管内皮细胞质膜膜泡关联蛋白(PLVAP)参与调控淋巴细胞与抗原进入淋巴结[67], 大分子的免疫原进入淋巴结后被淋巴囊下巨噬细胞及副皮质区的树突细胞吞噬, 而小分子抗原(小于70 kD)可直接进入淋巴结T及B细胞区, 在抗原提呈细胞到达前致敏淋巴结[68,69]. 淋巴管内皮细胞分泌很多趋化因子(包括CCL21)来调控免疫细胞的迁移, 包括其进入淋巴管及由被膜下淋巴窦向淋巴结髓质的迁移等[70,71]. 此外, 免疫细胞跨淋巴管迁移涉及多种细胞间连接黏附分子, 淋巴管内皮细胞所表达的黏附分子与免疫细胞跨血管迁移所需的黏附分子相同. 研究表明, 细胞间黏附分子-1 (intercellular cell adhesion molecule-1, ICAM-1)和血管细胞黏附分子-1 (vascular cell adhesion molecule-1, VCAM-1)在静息期的淋巴管内皮细胞呈低表达, 但肿瘤坏死因子α处理后可显著上调其水平; 利用ICAM-1及VCAM-1抗体可抑制树突状细胞黏附及跨淋巴管迁移. 促炎性因子也可快速上调E-选择素在淋巴管内皮细胞的表达, 通过与P-选择素糖蛋白配体(P-selection glycoprotein ligand-1, PSGL-1)的相互作用介导初始捕获过程中免疫细胞与内皮细胞间的可逆结合, 并可转换为通过VCAM-1与ICAM-1相互作用介导的紧密黏附, 以促进免疫细胞跨淋巴管的迁移. 另外, 淋巴管内皮细胞也可表达一些特殊受体(如CLEVER-1)介导免疫细胞迁移[72~78]. 利用转基因小鼠研究表明, 皮肤淋巴管发育缺陷导致疫苗接种诱导的体液免疫应答减

弱，脾脏T细胞有强应答但反应延迟[79]. 也有研究发现，淋巴结淋巴管内皮细胞可通过表达主要组织相容性复合物Ⅰ及免疫调节因子(包括PD-L1)，抑制$CD8^+$ T细胞激活，从而参与调节外周免疫耐受[77,80]. 最新研究发现，硬脑膜淋巴管可将脑脊液运送到颈淋巴结，从而参与脑脊液循环及脑组织中免疫细胞的转运[81].

3 淋巴管在重大疾病发生与发展中的病理机制

3.1 淋巴管发育缺陷的遗传机制

原发性淋巴水肿主要由遗传性淋巴管发育缺陷所致，目前已发现近20个基因的突变与淋巴管发育异常有关[37,46,82,83]. 遗传性淋巴水肿由Nonne在1891年第一次提出，Milroy于1892年描述了先天性淋巴水肿的家族分布，Meige于1898年报道了发生于青春期后常伴有急性蜂窝组织炎的淋巴水肿病例，而另外一种起始于青春期的淋巴水肿患者还伴有双行睫毛[62]. 研究表明，Nonne-Miroy淋巴水肿病人主要与VEGFR-3酪氨酸激酶失活突变有关，纯合突变的个体不能存活，杂合突变个体因淋巴管发育不全导致淋巴水肿[84]. 在淋巴水肿病人也发现有VEGF-C的突变[85]，并发现Hennekam淋巴管扩张-淋巴管水肿综合症与CCBE1突变有关[86]. 蛋白酪氨酸磷酸酶与VEGFR-3有相互作用，其突变可导致VEGFR-3过度激活及淋巴管发育异常，与淋巴水肿-后孔闭锁综合症有关[87]. 核转录因子FOXC2突变引起的单倍剂量不足与淋巴水肿-双睫综合症的发病有关，FOXC2突变也导致病人淋巴管瓣膜发育异常从而发生淋巴液返流现象[37]. 由于FOXC2存在多种突变体，目前对FOXC2不同突变引起淋巴管发育异常的分子机制还不清楚. 此外，导致淋巴管发育缺陷的基因还包括转录因子SOX18, GATA2, 以及联接蛋白CX47[3]. 虽然对淋巴水肿的发生机制有了深入的认识，但目前针对淋巴水肿的治疗主要还是依赖于物理性疗法及手术等，应用于淋巴水肿治疗的药物急待开发.

3.2 淋巴管与肿瘤转移

肿瘤内及其周围组织中常伴有大量的淋巴管新生[63,88]，抑制肿瘤相关的淋巴管生长可抑制淋巴管肿瘤转移[89~92]. 与组织器官发育过程中的淋巴管生成相比，肿瘤内淋巴管生长是无序的[63,93]. 首先，实体瘤中除血管内皮细胞外，肿瘤细胞、浸润肿瘤的免疫细胞，以及其他基质细胞都可以分泌淋巴管生长因子. 由于缺乏生长因子的浓度梯度，所以肿瘤内淋巴管没有正常的结构与成熟淋巴管网络图式. 其次，肿瘤内淋巴管分布不均，淋巴管生长通常发生在肿瘤坏死区或周边区域. 尽管大多数恶性实体瘤都表达淋巴管生长因子，临床上发现有淋巴管生长的肿瘤主要包括头颈部鳞状细胞癌、原位黑色素瘤、乳腺癌、肾细胞癌及胃癌等[63,94]. 利用肿瘤动物模型研究表明，肿瘤内淋巴管生成滞后于血管新生[90]. 这些证据表明，肿瘤淋巴管生成不仅受淋巴管生长因子介导的信号调节，而且还受肿瘤特异微环境因素的影响，包括血管异常渗漏导致的组织液压上升及肿瘤细胞增生引起的机械性压力等. 另外，虽有研究认为骨髓来源的细胞可分化成淋巴内皮细胞参与淋巴管形成，然而利用动物肿瘤模型并结合骨髓移植的研究表明，肿瘤淋巴管主要源于周围正常组织中已存在的淋巴管[95].

与肿瘤通过血行转移类似，肿瘤淋巴性转移过程包括肿瘤细胞脱离原肿瘤组织、入侵淋巴管并随淋巴液转运、逃避免疫监控以及在淋巴结建立转移灶. 尽管肿瘤淋巴管生成迟于血管，临床研究发现，在很多类实体瘤中，肿瘤淋巴结转移发生在病程的早期阶段[63,93]. 导致这一现象的可能原因包括以下4点：(ⅰ) 肿瘤细胞本身能分泌大量的淋巴管生长因子，诱导周围正常组织中的淋巴管向肿瘤生长，并伴有集合淋巴管的扩张，这些变化可促进肿瘤入侵淋巴管并转移到淋巴结[90]. (ⅱ) 前哨淋巴结内的淋巴管新生可促进淋巴性肿瘤转移. 除了随淋巴液从肿瘤中被运输到淋巴结的淋巴管生长因子，淋巴结内的免疫细胞也积极参与其淋巴管生长调控. 淋巴结B细胞与巨噬细胞等可分泌VEGF-C/D/A等因子，诱导淋巴结窦状隙内的淋巴管生成，而T细胞可通过分泌IFN-γ抑制淋巴管生成[96]. (ⅲ) 肿瘤细胞可模仿免疫细胞迁移的机制入侵淋巴管并发生转移. 已有研究表明，CCR7和CXCR4在人癌细胞内表达，而淋巴管内皮细胞表达其配体包括CCL21和CXCL12，从而促进肿瘤转移[97]. (ⅳ) 与血液循环系统中的低存活率相比，肿瘤细胞似乎更容易在淋巴管及淋巴结中存活和增殖. 有研究提示，淋巴管内皮细胞及肿瘤细胞分泌的CCL21参与调控肿瘤的微环境，促进免疫耐

受[98]. 由于淋巴管在肿瘤转移与微环境调控中的重要作用, 靶向肿瘤淋巴管可为恶性肿瘤治疗提供新的途径.

3.3 淋巴管与炎症

炎症是机体对病原微生物感染、组织损伤等有害刺激的一种复杂的生物反应, 包括免疫细胞浸润组织与炎症部位血管渗透性增加等, 组织炎症反应过程伴有活跃的淋巴管生长[99]. 炎症过程中浸润组织的免疫细胞包括巨噬细胞和粒细胞, 均可产生并释放淋巴管内皮细胞生长因子包括VEGF-C[100]等. 淋巴结中的B和T淋巴细胞也可分别产生调节淋巴管生成的促生长因子或负调控因子[96], 且炎性因子诱导的NFκB可促进淋巴管内皮细胞VEGFR-3的表达, 从而促进炎症过程的淋巴管再生[101]. 淋巴管通过吸收转运炎症引起的大量组织液与炎性细胞因子、死亡细胞的残骸及免疫细胞等, 从而参与炎症反应过程[63]. 在紫外辐射诱导的皮炎、肺支原体诱导的气管炎等动物模型中, 抑制淋巴管生长可加重炎症反应及组织的水肿程度[100,102], 而诱导淋巴管生长对炎症反应有抑制作用[103]. 然而, 也有研究表明移植器官的排异与淋巴管生长有关, 这可能由于淋巴管参与运送免疫激活的淋巴细胞浸润移植组织所致, 抑制淋巴管新生可促进器官移植后的存活[104,105]. 因此, 该方向的深入研究具有重要的临床意义与应用前景.

3.4 淋巴管与心血管疾病

动脉粥样硬化是一种炎症性疾病, 由动脉内膜损伤等因素导致内皮细胞激活. 其病理发展过程中除有T淋巴细胞侵润以及平滑肌细胞增生等过程外, 最显著的特征是招募单核细胞分化成巨噬细胞后吞噬过量胆固醇及其代谢物, 形成相应固醇酯异常堆积的泡沫细胞, 进而在动脉管壁内膜形成纤维脂质斑块[106,107]. 研究发现, 巨噬细胞中的胆固醇也可外排, 即细胞质中的胆固醇酯水解成游离胆固醇, 由ATP结合盒转运蛋白包括ABCA1, ABCG1及清道夫受体SR-B1等运出细胞外, 并与细胞外载脂蛋白受体包括apo-AI及成熟型高密度脂蛋白(high-density lipoprotein, HDL)结合, 由淋巴管进入血液循环, 经肝脏处理后随胆汁及肠道排泄物排出, 以上过程称为胆固醇逆向运输[108]. 有趣的是, 组织间隙中的高密度脂蛋白主要通过淋巴管进入血液循环, 淋巴管内皮细胞表达HDL受体包括SR-B1[60]. 在*ApoE*基因敲除小鼠诱导淋巴管新生可促进胆固醇逆向运输以降低外周组织中胆固醇的储备, 而抑制淋巴管生长或淋巴管发育缺陷则阻断该过程[61,109]. 在淋巴管发育缺陷并同时缺失低密度脂蛋白受体与载脂蛋白B48的小鼠, 血浆中胆固醇含量及动脉粥样硬化发生率显著升高[110]. 高胆固醇血症及肥胖也可直接损害淋巴管功能[111,112]. 另外, 利用心肌梗死动物模型研究表明, 心肌梗死病理过程中伴有淋巴管新生, 利用外源性VEGF-C诱导淋巴管生长可改善心梗后心肌的功能[8]. 因此, 促进淋巴管功能特别是病灶组织周围淋巴管生长对于防治心血管疾病包括动脉粥样硬化有积极作用.

4 我国淋巴管研究的基金资助情况及研究进展

近年来, 针对淋巴管的研究已逐渐引起各国的关注, 相关机构也加强资助开展相关的研究. 美国国立卫生研究院近10年来共资助了167项淋巴管相关的研究项目, 近3年来在淋巴管发育及淋巴管与肿瘤、炎症、脂质代谢等研究方向的资助有了明显的加强. 国家自然科学基金委员会是我国支持自然科学基础研究重要的资助机构之一, 近年来也逐渐加大资助淋巴管领域的基础研究, 但总体上仍较为薄弱, 近10年来只有102项淋巴管相关的项目获得资助. 为了进一步引导和提升我国淋巴管相关的研究, 国家自然科学基金在2016年度鼓励开展淋巴管系统的发育与功能研究, 加强资助在淋巴管系统生成过程的调控机制、成熟稳态维持机制、体液循环中淋巴液与血液的关系、淋巴管系统对脂质代谢的功能作用、淋巴管系统发挥的免疫防御作用以及淋巴管系统相关的重大疾病机理等方面开展深入的研究工作. 2016年, 共有79项淋巴管相关的申请项目, 分布于肿瘤学、免疫学、循环科学及医学影像学等学科, 结果有17项相关的项目获得资助, 总体上相对历年有了明显的增加.

此外, 2016年2月, 国家自然科学基金委员会医学科学部联合中国科学院上海生物化学与细胞生物学研究所举办了“淋巴管系统与相关疾病”战略研讨会, 会议充分研讨了我国淋巴管系统与相关疾病的研究和发展现状, 分析了我国在该领域与国际上相关研究的差距和自身的优势与特色, 明确了淋巴管系统与相关疾病在基础与临床医学研究中不可或缺

的地位，对于今后更好地推动我国淋巴管相关研究具有重要的学术与战略意义.

得益于我国在该研究领域投入的增加，淋巴管及相关学科的研究也在快速发展，取得了一些具有较高水平的原创性研究成果. 有研究发现，胃癌淋巴管新生程度与病人预后呈显著正相关[113]. 阻断TIE2介导的信号途径能显著抑制肿瘤淋巴道转移，但对肿瘤的淋巴管新生没有明显的抑制作用[114]. 同时阻断VEGF-A与VEGF-C介导的信号途径可抑制肿瘤淋巴管与血管生长及肿瘤转移[115]. Endostatin通过作用于淋巴管内皮细胞表面受体Nucleolin对肿瘤淋巴管新生与肿瘤转移起显著抑制作用[116]. SIX1通过TGFβ介导的信号途径促进肿瘤VEGF-C表达及肿瘤淋巴管生成[117]. 此外，国内多个研究组已制备一系列靶向淋巴管关键调控基因的遗传改造动物模型. 利用靶向VEGFR-3配体结合区的条件性基因敲除小鼠模型探讨了VEGFR-3信号途径在淋巴管与血管发育中的不同作用与机制[25]. 敲除Akt1导致其毛细淋巴管内皮细胞显著减少及管腔变细、集合淋巴管的平滑肌细胞招募异常，以及淋巴管瓣膜发育异常[118]. 利用靶向TIE信号途径的条件性基因敲除小鼠系统分析了ANGPT2/TIE1在淋巴管网络成熟重塑过程中的作用，且发现该生物学功能不依赖于TIE2介导的信号[50]. 利用斑马鱼(*Danio rerio*)模型的研究发现，Ras蛋白激活因子RasGRP1能够调节斑马鱼淋巴管的早期发育，并与血管内皮生长因子受体VEGFR-3协同调节淋巴管的生成[119]. 另外，临床相关研究发现，在中国人群的淋巴水肿病人发现淋巴管关键调控基因*Foxc2*的突变体，并对原发性淋巴水肿淋巴管畸变的形态学进行了分类[120].

总体来说，我国淋巴管研究尚处于起步阶段，有待于在该领域加大投入，针对淋巴管系统发育与稳态维持、淋巴管的生理功能、淋巴管在重大疾病发生与发展中的病理机制、中国人群淋巴水肿的遗传与环境因素，以及淋巴系统研究的相关技术开发与应用等开展深入研究，以获得在淋巴管生物学与淋巴医学方面的突破性进展，为临床相关疾病的诊治提供新的手段.

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Summary for “淋巴管系统相关研究现状与展望”

Progress and prospect of lymphangiogenesis research

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During the last twenty years, we have witnessed a rapid progress in the field of lymphatic vascular biology. The increase of lymphatic research has greatly deepened our understanding of the lymphatic system in health as well as in diseases. This review starts with the description of the current understanding of the mechanism underlying lymphatic formation and remodeling in development. In mammals, lymphatic vessel development initiates with the specification of lymphatic endothelial cells from a population of venous endothelial cells in the lateral parts of the anterior cardinal veins. This is followed by the formation of lymph sacs, which undergoes expansion into the primitive lymphatic plexus by the process of lymphangiogenesis. The primary lymphatic network is further remodeled into a mature lymphatic system composed of lymphatic capillaries and collecting lymphatics containing intraluminal valves as well as smooth muscle cell coverage. Several key factors and pathways have been identified to participate in the process, including lymphangiogenic growth factors and receptors, extracellular matrix proteins and cell junction molecules, intracellular signal mediators and transcription factors. It is interesting to find out how these factors coordinate to control collecting vessel formation and maturation, and whether they work in the same pathway or in different pathways controlling specific cellular programs. Secondly, the authors summarize the physiological functions of lymphatic system, including the essential role of lymphatic system in the maintenance of tissue fluid homeostasis. Defective lymphatic development or damage of the lymphatic system resulting from surgery or infection leads to lymphedema. In immune system, lymphatic vessels are crucial for the leukocyte trafficking from peripheral tissues to their draining lymph nodes and for the drainage of soluble antigens. Furthermore, the absorption of dietary nutrients is critically dependent on the lymphatic vessels in intestines, also known as lacteals in intestinal villi. Finally, the authors have discussed the involvement of lymphatic system in several diseases including tumor metastasis, inflammation and cardiovascular diseases. It has also been well established that tumor associated lymphangiogenesis promotes lymphogenous tumor metastasis. Although the molecular players responsible for lymphatic vessel growth is similar in development and tumor, there are distinct characteristics of tumor-associated lymphangiogenesis, including the lack of lymphangiogenic growth factor gradient in tumor. Therefore, tumor-associated lymphatics are patchy, disorganized without a hierarchical vascular pattern, and also not homogenously distributed within tumors. In addition, inflammation is often associated with profound lymphatic vessel growth and remodeling, and there are also evidence showing that the abnormal lymphatic growth is implicated in cardiovascular diseases. In spite of the recent progress in the research field of lymph-vascular biology, there is still lack of effective drugs for the prevention and treatment of lymphedema and lymphatic related diseases. Thus, continued support and further increase in research investment in this field are very much wanted to better understand the cellular events and molecular players involved in lymphatic vessel growth and function at both physiological and pathological conditions.

lymphangiogenesis, fluid homeostasis, immune surveillance, lipid metabolism, lymphedema, tumor metastasis

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