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CC趋化因子与心肌梗死的研究进展*

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摘要 CC类趋化因子亚家族是趋化因子家族中成员最多、研究最广泛的一大类细胞因子，其主要功能是参与炎症细胞激活、迁移、黏附等病理生理过程. 大量研究表明，CC类趋化因子亚家族成员参与了心肌梗死后病理过程的各个阶段. 其中研究最为深入的是单核细胞趋化蛋白1（monocyte chemoattractant protein-1，MCP-1）及其受体CC趋化因子受体2（CC chemokine receptor 2，CCR2）. MCP-1和CCR2在心肌梗死后炎症期、增殖期及疤痕愈合期都发挥了重要作用从而影响梗死后心室重构. 近年来，CC类趋化因子亚家族其他成员亦被逐渐揭示参与了心肌梗死的发展. 本文结合以往大量文献，就CC类趋化因子亚家族在心肌梗死各个阶段中的作用，尤其是梗死后各期对于心室重构的影响进行综述，以期为今后的CC趋化因子研究提供方向，为相关疾病的预防和治疗研究提示潜在的药物靶点.

关键词 CC类趋化因子亚家族，心肌梗死，炎症，心室重构
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心肌梗死是急性冠脉综合征最严重的恶性心血管事件. 急性心肌梗死发生时常伴随严重的炎症反应，大量心肌细胞坏死，诱导并释放大量细胞因子及趋化因子[1-3]，在梗死后，心脏固有的巨噬细胞、淋巴细胞及肥大细胞首先被招募并浸润入梗死心肌，穿过坏死肌纤维并逐渐吞噬梗死的心肌，直至坏死心肌、基质碎片被彻底吞噬[4]，同时中性粒细胞从血管内浸润入梗死区，吞噬坏死心肌碎片，并限制梗死区扩大[5]，浸润入梗死区的中性粒细胞同时可释放大量的活性氧，导致梗死早期细胞损伤[6]，此时期称为炎症期[7]. 随后，单核/巨噬细胞数量逐渐减少，炎症反应逐渐受到抑制，大量活性氧产生，肌成纤维细胞和内皮细胞被激活，进入增殖期[7]. 肌成纤维细胞的激活及内皮细胞的增殖，分泌出大量的基质蛋白，随后发生凋亡，形成胶原疤痕，梗死区逐渐被疤痕组织取代，称为疤痕愈合期，各期之间相互重叠[7-8]. 在疤痕愈合期亦存在着炎症反应，最近研究表明，中性粒细胞可促进巨噬细胞表型向抗炎表型转换，从而促进疤痕愈合[9-11]，而炎症期、增殖期及疤痕愈合期的变化可直接影响梗死后心室重构. 大量研究表明，心肌梗死后炎症反应减轻使梗死面积减少，增殖期和疤痕愈合期基质金属蛋白酶（matrix metalloproteinases，MMPs）增加，这些变化都与不良心室重构及严重心梗后并发症相关[7, 12-14].

趋化因子是一大类分子质量在8~14 ku且具有十分相似三级结构的小分子质量蛋白[15]. 多数趋化因子含有4个半胱氨酸，其中第一、三和二、四半胱氨酸分别形成了2个二硫键. 根据前两个半胱氨酸之间氨基酸的数量，趋化因子分为CC、CXC和CX3C亚家族. 趋化因子发挥生物学作用往往需要与靶细胞表面表达的趋化因子受体结合，趋化因子受体多为跨膜多螺旋G蛋白[16]，而且一种趋化因子可结合多种受体，同种受体亦可结合多种趋化因子. 趋化因子及其受体的主要生物学作用为通过

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介导炎症细胞的迁移、黏附、脱颗粒及凋亡而引起组织炎症反应[17-19]. 而趋化因子及受体参与了心肌梗死后的反应过程，在炎症期主要作用于炎症细胞发挥其趋化性作用，可介导单核细胞、中性粒细胞等炎症细胞向梗死区的迁移、浸润和黏附[17]，而在增殖期和疤痕愈合期可作用于内皮细胞、肌成纤维细胞等，但其具体的作用机制尚未完全阐明[20].

CC类趋化因子亚家族是趋化因子中成员最多的家族，目前发现有28个成员及其受体（表1）. 其中，研究最为深入的是单核细胞趋化蛋白1（monocyte chemoattractant protein-1，MCP-1）及其受体CC趋化因子受体2（CC chemokine receptor 2，CCR2）. 大量研究表明，MCP-1和CCR2参与了梗死时中性粒细胞和促炎单核细胞向梗死区的浸润和募集[21-22]. 而近年来越来越多研究者更加关注MCP-1/CCR2在梗死后心室重构中的作用. 随着研究的深入，发现CC家族其他成员亦参与了心肌梗死不同时期的病理过程. 本文就近年来CC类趋化因子亚家族成员在心肌梗死不同时期的作用，尤其是梗死后各期对于心室重构的影响进行综述，以期为今后的CC趋化因子研究提供方向，为相关疾病的预防和治疗研究提示潜在的药物靶点.

1　MCP-1/CCR2

早在20世纪90年代，临床研究就发现，心肌梗死病人血清中MCP-1在胸痛发生3 h时就有明显的增高，9 h达到高峰并持续24 h[23]. 其后大量的临床研究证实了在不稳定心绞痛及心肌梗死病人血

Table 1　Properties of the CC chemokines

表1　CC类趋化因子亚家族成员

学名	人源属名	鼠源属名	表达形式	受体
CCL1	I-309	TCA-3/P500	诱导	CCR8
CCL2	MCP-1/MCAF	MCP-1	诱导	CCR2
CCL3	MIP-1α	MIP-1α	诱导	CCR1，CCR5
CCL4	MIP-1β	MIP-1β	诱导	CCR5
CCL5	RANTES	RANTES	诱导	CCR1，CCR3，CCR5
（CCL6）	未知	C10/MRP-1		未知
CCL7	MCP-3	MARC?	诱导	CCR1，CCR2，CCR3
CCL8	MCP-2	MCP-2?	诱导	CCR3，CCR5
CCL9	未知	MRP-2.MIP-1γ		
CCL10	未知	CCF18		
CCL11	Eotaxin	Eotaxin	诱导	CCR3
（CCL12）	未知	MCP-5	诱导	CCR2
CCL13	MCP-4	未知	诱导	CCR2，CCR3
CCL14	HCC-1	未知		CCR1，CCR5
CCL15	HCC-2/MIP-1δ	未知		CCR1，CCR3
CCL16	HCC-4/LCC-1	未知		CCR1，CCR2
CCL17	TARC	TARC/ABCD-2	诱导	CCR4
CCL18	DC-CK1/PARC	未知	固有	未知
CCL19	MIP-3β/ELC-exodus-3	MIP-β/ELC-exodus-3	固有	CCR7
CCL20	MIP-3α /LARC/ exodus-1	MIP-3α /LARC/ exodus-1	固有	CCR6
CCL21	6Ckine/SLC/ exodus-2	6Ckine/SLC/ exodus-2	固有	CCR7
CCL22	MDC/STCP-1	ABCD-1	两者	CCR4
CCL23	MPIF-1/CKβ8	未知		CCR1
CCL24	Eotaxin-2/MPIF-2	MPIF-2	诱导	CCR3
CCL25	TECK	TECK	固有	CCR9
CCL26	Eotaxin-3	未知	诱导	CCR3
CCL27	CTACK/ILC	ALP/CTACK	固有	CCR10
CCL28	MEC	未知		CCR3，CCR10

?：还未确定.

清中MCP-1的表达量明显增高[24-28]，近年进一步研究揭示，在心肌梗死病人心脏组织标本中MCP-1在梗死发生极早期（0～4 h内）表达量明显增高，而在早期（6～8 h之间）表达量逐渐减少[29]. MCP-1表达量增多，促进了中性粒细胞、单核/巨噬细胞等大量炎症细胞向梗死区的浸润. 但在心脏特异性过表达MCP-1，并不能诱导促炎因子的表达[30]，全身性敲除MCP-1基因的小鼠在梗死区中性粒细胞的浸润亦没有增加，但可减少单核细胞向巨噬细胞表型的分化[31]. MCP-1在心肌梗死极早期即可招募心肌单核/巨噬细胞进入梗死区使梗死面积减小而起到保护心脏的作用[32]. 而且在心肌梗死早期，MCP-1可促进梗死区侧枝动脉的生成[33-34]. 因此在炎症期，MCP-1主要通过：a. 促进单核/巨噬细胞向梗死区迁移、浸润，吞噬梗死心肌；b. 促进梗死区侧枝动脉的生成，从而起到保护心脏的作用. 在增殖期、疤痕愈合期，MCP-1亦发挥了重要的作用，但其作用是否有益存在很大的争议. 降低心肌梗死小鼠体内MCP-1的表达可降低小鼠的死亡率，减轻左心室扩张及收缩功能不全，其机制为减少巨噬细胞的浸润，减少心肌肿瘤坏死因子α（TNF-α）和转化生长因子β（TGF-β）基因的表达从而减轻间质纤维化[35]. 敲除MCP-1的心肌梗死小鼠梗死区单核细胞浸润减少，迁移速度缓慢，梗死区分泌的细胞因子减少，巨噬细胞分化异常，肌成纤维细胞减少，心肌纤维化减轻，可明显减轻梗死后心室重构[31]. 在小鼠中敲除MCP-1后巨噬细胞浸润减少，间质纤维化减少，明显改善了心室功能不全[36]. 临床研究亦表明，MCP-1可促进缺血再灌注后心肌损伤及梗死后心室重构[28]. 以上结果表明，MCP-1对梗死后左心室功能不全及重构是有害的. 但亦有报道认为MCP-1具有心脏保护作用. 体外实验显示，MCP-1在低氧条件下可显著降低心肌细胞的死亡[37]. 而在小鼠心脏特异性过表达MCP-1可诱导巨噬细胞浸润、新生血管生成，心脏分泌IL-6以及心脏肌成纤维细胞增多，这些都有利于疤痕生成及减轻心肌梗死后左心室功能不全及心室重构[38]. 研究表明，心肌梗死疤痕愈合期，非梗死区MCP-1表达量增加并伴随巨噬细胞的浸润[35]，随后研究显示，在梗死和非梗死的交界区，MCP-1的表达量及巨噬细胞的浸润程度比非梗死区更高，但其机制并未阐明[39]. 一项心肌梗死病人的队列研究显示，MCP-1的作用具有很强的时间依赖性，早期MCP-1表达增高可促进梗死的愈合和修复，而MCP-1持续表达增高则会加重炎症反应和心肌纤维化，引起严重的心室不良重构[40]，引起MCP-1作用时间依赖性可能与相邻的非梗死区炎症因子、MMPs的旁分泌有关，也可能存在其他趋化因子家族的代偿性作用，但具体机制尚未阐明. 最新一项临床队列研究显示，心肌梗死患者入院时MCP-1水平相对较低组，梗死区单核细胞浸润减少不能及时将坏死心肌碎片清除导致愈合延迟而引发不良的心室重构，因此其罹患梗死后严重并发症的几率及致死率、复发率较高[41]，另一项研究亦表明，MCP-1水平相对较低的患者，梗死区心肌损伤更加严重，因此出现梗死后严重并发症的几率增高[42]. 作者推测MCP-1对梗死后的调节作用亦取决于心肌损伤的程度.

综上所述，MCP-1在心肌梗死早期表达量明显增加. 在心肌梗死炎症期，MCP-1主要发挥其趋化性作用，促使中性粒细胞、单核/巨噬细胞向梗死区浸润，吞噬梗死的肌纤维，并可促进侧枝动脉的生成. 随后炎症反应被抑制，MCP-1表达量逐渐减少，巨噬细胞浸润减少，细胞因子分泌减少，肌成纤维细胞减少，心肌纤维化减轻，这些被认为有利于疤痕愈合及心室重构. 但亦有研究表明，在心脏过表达MCP-1也具有改善心室重构的作用. 因此，MCP-1在心肌梗死后对心室重构的影响目前还存在争议. 有学者认为MCP-1局部表达量的不同对实验结果影响很大，有些研究者认为这种异质性主要原因为物种的不同，还有学者认为是与疾病发生时局部的MCP-1表达量有关. 心肌梗死后心室重构是一个逐渐发展的过程，在这个过程中梗死的面积及梗死区及非梗死区所占的比例有一定的个体性，而在不同的实验研究中往往以时间点来评价MCP-1对于梗死后的影响，可能存在个体差异性的误差，因此，MCP-1研究的重点为阐明这种异质性并尽可能地避免个体差异性，进而找到理想的模型来模拟人类心肌梗死发病的过程，为疾病的诊疗及药物靶点提供实验支持.

CCR2是MCP-1的主要受体，表达于内皮细胞和肌成纤维细胞[43-44]. 大量研究表明，其与MCP-1相似，对于心肌梗死后心室重构具有重要作用. 在小鼠梗死区肉芽组织中CCR2表达明显增高[31]. 研究揭示，在小鼠体内敲除CCR2可改善心肌梗死后左室扩大及左室功能不全，其机制主要为减少梗死区巨噬细胞的浸润从而抑制基质金属蛋白酶8（matrix metalloproteinase-8，MMP-8）、基质金属蛋

白酶9（matrix metalloproteinase-9，MMP-9）及基质金属蛋白酶13（matrix metalloproteinase-13，MMP-13）的活性及上调基质金属蛋白酶抑制剂（matrix metalloproteinase inhibitor，TIMP-4）蛋白的表达[45]. 随后研究显示，在小鼠体内敲除CCR2改善心肌梗死心室重构的机制不仅是抑制MMPs的表达，而且还与巨噬细胞产生的氧化应激反应有关[46].

MCP-1/CCR2在梗死炎症期对于炎症细胞的招募有利于疾病的预后，但研究表明，在增殖期及疤痕愈合期过度炎症及炎症反应时间延长，可导致不良的心室重构及心室破裂、心力衰竭等严重的并发症. 而在增殖期及疤痕愈合期，大量研究显示下调MCP-1/CCR2的表达可改善心室重构，因此大量学者着力于研究其作为药物靶点改善心肌梗死后心室重构的生物学作用. 研究者利用MCP-1竞争性抑制剂抑制MCP-1与CCR2受体结合后，发现小鼠心脏的梗死面积减小，单核细胞的浸润、梗死区胶原蛋白及肌成纤维细胞的含量明显降低，改善了心室重构，证实MCP-1/CCR2可作为治疗心肌梗死的药物靶点[47-48]. 而利用小干扰RNA沉默CCR2基因表达，可明显减少小鼠心脏梗死区单核细胞的浸润，减轻梗死灶炎症反应，改善心肌梗死后左室重构[49]. 为了提高药物的靶向性，最近研究者利用脂质微胶粒靶向抑制CCR2的表达，结果显示可明显抑制单核细胞数量从而改善心肌梗死的梗死面积及心功能[50]. 目前MCP-1/CCR2作为药物靶点的研究只限于动物实验，如进入临床试验阶段还要解决很多问题，如提高药物的靶向性，用药的准确时机，药物的安全性及有效性等. 而这些问题的解决有待后续对MCP-1/CCR2在心肌梗塞发病过程中具体机制的细化研究，及大量可靠的动物实验来证实.

2　CCR5及其配体

CCR5主要表达于巨噬细胞表面，是CCL3、CCL4和CCL5的共同受体，同时对CCL2具有较低的亲和力[45，51]. 在小鼠心肌梗死区可见CCR5表达量的明显增高[31，52]. CCR5主要调控巨噬细胞相关炎症反应，而在心肌梗死发生中，CCR5主要作用为抑制巨噬细胞的浸润及过度的炎症反应，从而减少细胞外基质的降解及不良的心室重构，其机制主要为激活并募集了大量的调节性T淋巴细胞[53-54]. 目前研究显示，CCR5在心肌梗死后炎症控制中发挥巨大的作用，早期可调控巨噬细胞向梗死区的浸润，随后激活T淋巴细胞，防止炎症过度扩大，从而预防心室破裂及严重的心室不良重构. CCL5，即RANTES，主要表达于T细胞、内皮细胞、血小板及平滑肌细胞，其功能主要为介导T细胞的迁移、归巢及增殖[55]. 临床研究表明，心肌梗死患者血清中CCL5的水平与心肌受损的范围和程度有关，因此可作为心肌梗死后心源性休克和急性心力衰竭等严重并发症的生物标志物[56]. 实验动物模型研究显示，在梗死1天后梗死区CCL5的表达量就明显增高，3～7天后血清中表达量也明显增高，而在心肌梗死早期给予CCL5抗体后梗死面积明显缩小，且减少了心肌梗死后心力衰竭的发生并降低了小鼠的死亡率，但可引起免疫反应紊乱[57]. CCL3，又称为巨噬细胞炎症蛋白1α（macrophage inflammatory protein-1α，MIP-1α），作用于单核细胞. 研究表明，在心肌梗死及不稳定性心绞痛患者血清中CCL3明显增高，且在心肌梗死模型小鼠体内CCL3表达明显上调[52，58]. CCL4，即巨噬细胞炎症蛋白1β（macrophage inflammatory protein-1β，MIP-1β），是单核细胞趋化因子，主要由正常T细胞表达并分泌. 在心肌梗死模型小鼠体内，CCL4 mRNA表达可出现短暂上调[52]，临床研究表明，CCL4可联合纤维蛋白原预测冠状动脉病变向心肌梗死的转变[59]. 但CCL3及CCL4在心肌梗死发病中的作用及具体的机制尚未有进一步的研究.

3　CCR9/CCL25

CCR9主要表达于淋巴细胞、树突状细胞及单核/巨噬细胞，其唯一的配体为CCL25[60-61]，主要在胸腺和小肠组织中表达[62]. 研究表明，小鼠心肌梗死后CCR9的表达量明显增高，敲除CCR9后可降低心肌梗死后小鼠的病死率，减小梗死面积，改善心脏功能，CCR9可通过NF-κB和MAPK信号通路干预梗死后心室重构，并且敲除CCR9后可改善心脏心梗后电重构，因此CCR9/CCL25在梗死后炎症细胞的浸润和心脏重构中发挥了重要作用[63]. 目前对于CCR9/CCL25的研究还不是很多，而且缺乏临床研究，鉴于目前动物研究的发现，有理由相信CCR9/CCL25具有成为疾病预防及药物靶点的潜质.

4　CCR1及配体

CCR1表达于血管内皮细胞上，其主要配体为

CCL3和CCL5，这两种趋化因子主要由活化的血小板释放，CCR1及其配体主要介导炎症细胞的浸润[64-65]. 在敲除CCR1的心肌梗死模型小鼠梗死区，中性粒细胞浸润减少，单核细胞浸润增加，胶原蛋白及肌成纤维细胞合成增加，从而明显减轻心肌损伤及坏死，促进疤痕愈合，改善心室重构[66].

5 CCL21/CCR7

CCL21及其受体CCR7表达于T淋巴细胞并广泛表达于纤维母细胞、血管平滑肌细胞和内皮细胞，可介导T淋巴细胞向外周组织迁移并可调节血管炎症、血管平滑肌细胞的增殖及基质重构[67-70]，亦有研究表明CCL21/CCR7可促进单核细胞的黏附及向外周组织的浸润[71]. 动物实验表明，心肌梗死后1～7天血清中的CCL21及梗死区的CCL21和CCR7含量明显增高，降低CCL21表达水平可减少梗死面积、减少中性粒细胞及巨噬细胞的浸润、短暂减少梗死区MMP-9的表达及胶原蛋白的含量，从而限制心脏扩大及心功能不全等心梗后并发症的发生[72]. CCL21/CCR7在心肌梗死中的研究并不多，而且实验研究还停留在动物模型上，初步的动物实验结果显示CCL21/CCR7对于心肌梗死的发生和发展具有明显的影响，其对于疾病的诊疗及药物开发的具体作用和价值尚有待进一步实验验证及阐明.

6 CKLF1/CCR4

趋化因子类因子1（chemokine like factor 1，CKLF1）是新近发现的一种趋化因子家族成员，分子质量10 ku，具有典型的CC趋化因子亚家族分子结构，其序列中存在两个连续的半胱氨酸残基，但与CC趋化因子亚家族成员相比其缺少C端半胱氨酸残基[73]. CKLF1与CCR4具有较高的亲和力，CKLF1可作用于淋巴细胞、巨噬细胞、神经细胞等[74]. 早前一项临床研究显示，CKLF1可改善心肌梗死后患者心功能[75]. 此外，研究显示，CKLF1可动员心肌梗死后小鼠外周血中的$CD3^+$细胞进入梗死区，修复受损心肌[76]. 我们课题组前期大量研究表明，下调CKLF1表达水平，可减少脑卒中后梗死区中性粒细胞的浸润，抑制炎症反应，减少脑卒中梗死面积及脑卒中后并发症心肌梗死的发生[77-80]. 以上研究结果提示，CKLF1及其受体CCR4可能在心肌梗死发生及发展中起到重要作用，但还需要大量的实验支持及机制研究.

7 结语及展望

CC类趋化因子亚家族在心肌梗死发生的各个阶段都发挥了重要作用. 在梗死灶内CC类趋化因子亚家族都会出现瞬时表达量的增高. 心肌梗死早期，主要发挥对于炎症细胞的趋化性作用，炎症细胞的有序激活及抑制直接影响疾病的严重程度，尤其是巨噬细胞的过度激活和浸润范围增大，直接影响随后的增殖期和疤痕愈合期的变化从而影响心室重构[2]. CC类趋化因子亚家族对于炎症细胞的激活和浸润至关重要，MCP-1/CCR2可促进单核/巨噬细胞、中性粒细胞在梗死早期向梗死区浸润，目前研究认为，梗死早期巨噬细胞及中性粒细胞的浸润可限制梗死区域的扩大，有利于疾病的预后. 而CC家族其他成员亦不同程度参与了早期炎症细胞的激活和浸润，如CCR5可抑制巨噬细胞过度浸润及过度的炎症反应. 在心肌梗死增殖期和疤痕愈合期，大多数CC趋化因子家族成员可影响成纤维细胞向肌成纤维细胞转化，促进新生血管的产生，与MMPs相互作用影响胶原蛋白的产生，从而影响心室重构（图1）. 大多数学者认为，MCP-1/CCR2在心肌梗死后心室重构中作用最大，最具有成为药物靶点的潜力，但由于MCP-1/CCR2在心肌梗死后作用具有时间依赖性，因此如作为药物靶点需明确用药的时间窗. CC家族成员CCL5与趋化因子其他家族成员CXCL4可发生相互作用，使梗死区中性粒细胞和单核细胞浸润减少，从而减轻心肌损伤[81]，因此在心肌梗死发生后各趋化因子家族成员之间的相互作用可成为未来研究的方向. 普遍认为其他的CC家族成员在敲除后可改善心肌梗死后疤痕愈合及心室重构，但研究还不够深入，事实上，大多数CC家族其他成员在肿瘤的发生及转移中具有重要作用，如CCR9、CCL7、CCL11被认为可影响多种肿瘤的发生及转移，其机制主要为介导炎症细胞的激活、分化及浸润[82-85]. 而CC类趋化因子亚家族在心肌梗死中亦是通过介导炎症细胞而完成重要作用的，因此，CC家族其他成员在心肌梗死中的作用是发掘心肌梗死发病机制的方向，且有成为疾病预防、诊断及药物靶点的巨大潜力.

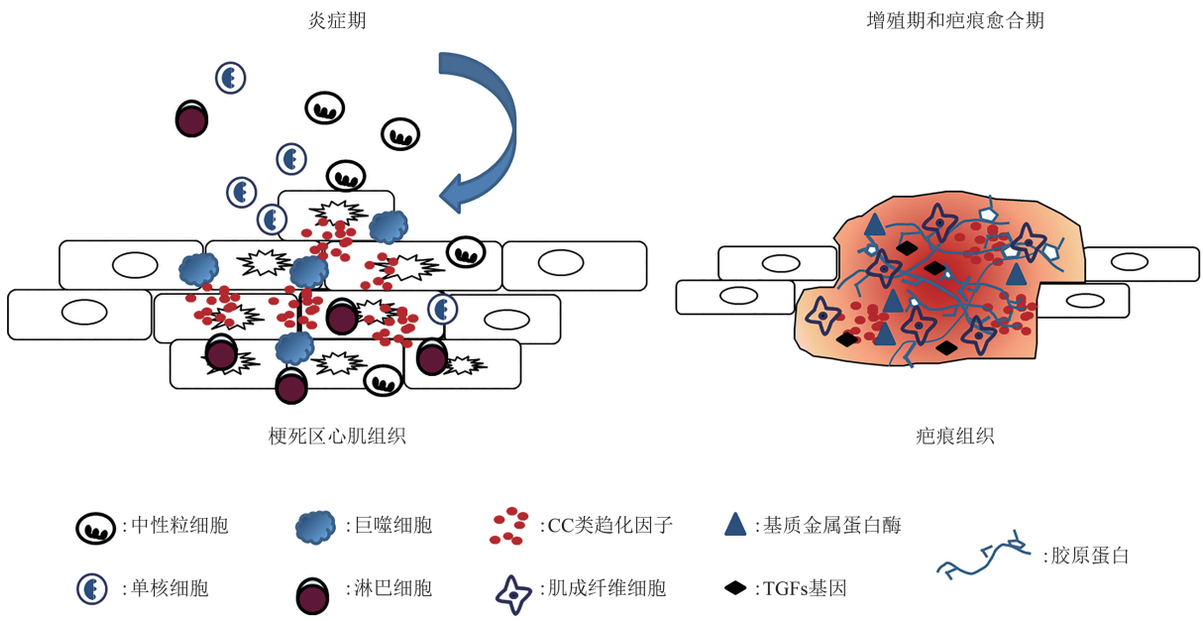

Fig. 1　Effects of CC chemokines on healing myocardial infarcts

图1　CC类趋化因子在心肌梗死各阶段的作用示意图

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The Roles of CC Chemokine in Myocardial Infarction*

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Abstract　The CC chemokines is the largest and most widely studied group of chemokines, which play a critical role in inflammatory leukocyte locomotion, trafficking and adhesion. The chemokine CC subfamily are involed in the pathogenesis of myocardial infarction. Monocyte chemoattractant protein-1(MCP-1) and its receptor CC Chemokine receptor 2 (CCR2), as most studied chemokine, plays an important role in post-infarction inflammation, proliferation and scar formation, thus affecting ventricular remodeling after myocardial infarction. In recent years, other members of the CC chemokines have been gradually revealed to be involved in the development of myocardial infarction. This article reviews the role of CC chemokines in various stages of myocardial infarction, especially the effects on ventricular remodeling after myocardial infarction, in order to provide direction for future experimental research and novel strategies in the treatment of patients with myocardial infarction disease.

Key words　CC chemokine, myocardial infarction, inflammation, ventricular remodeling

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