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整合素LFA-1与其配体ICAM-1的生理功能及相关疾病

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摘要 整合素淋巴细胞功能相关抗原-1与其主要配体细胞间黏附分子-1的相互结合所介导的细胞与细胞之间以及细胞与细胞外基质之间的黏附在免疫反应和炎症反应中都起重要作用。LFA-1与ICAM-1对T淋巴细胞的活化和克隆增殖起着不可缺少的作用。LFA-1与ICAM-1还参与启动免疫突触的形成、介导淋巴细胞的归巢等多种生理过程。另外, 风湿性关节炎、器官移植后发生的急性排斥反应、冠心病和寻常型银屑病等许多疾病的发生发展都和LFA-1与ICAM-1的相互作用有关。该文重点介绍了LFA-1与其配体ICAM-1参与的主要生理功能以及与此相关的几种疾病。

关键词 整合素; LFA-1; ICAM-1; 免疫突触; 淋巴细胞归巢; 类风湿性关节炎; 移植排斥

The Biological Functions of Integrin LFA-1 and Its Ligand ICAM-1 and the Related Diseases

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Abstract The binding of lymphocyte function-associated antigen-1 (LFA-1) to its major ligand intercellular adhesion molecule-1 (ICAM-1) can mediate cell-cell and cell-extracellular matrix adhesion, which plays an important role in immune response and inflammation. The combination of LFA-1 and ICAM-1 is involved in many kinds of physical processes, including T lymphocyte activation and clonal proliferation, the initiation of the immune synapse' formation, and mediation lymphocyte trafficking. In addition, it is related to the occurrence and development of many diseases, such as rheumatoid arthritis, organ transplantation acute rejection, coronary heart disease, and psoriasis vulgaris. In this review, we introduced the biological functions of LFA-1 and ICAM-1 and several diseases that associated with their interaction.

Key words integrin; LFA-1; ICAM-1; the immune synapse; lymphocytes homing; rheumatoid arthritis; graft rejection

1 引言

淋巴细胞功能相关抗原-1(lymphocyte function associated antigen-1, LFA-1)属于整合素家族, 整合素是一类重要的细胞黏附分子, 是由α和β两个亚基通过非共价键组成的异源二聚体, 整合素可以通过其胞内区与胞内的细胞骨架蛋白和信号分子结合, 通过由内到外(inside-out)和由外到内(outside-in)双向传递跨膜信号[1-4]。这些过程伴随着整合素对其配体亲和力的改变。整合素的这些特性对于生物体的免疫反应、细胞迁移、免疫细胞的组织定位、凝血、组织愈伤、组织和器官的发育, 甚至神经系统的正常功能等都至关重要[5-10]。LFA-1作为整合素的一员具有同样的特性。LFA-1是由α链CD11a和β链CD18组成的异源二聚体[11], 分布于T、B淋巴细胞、单核、巨噬细胞及中性粒细胞表面。细胞间黏附分子-1(intercelluar adhesion molecule-1, ICAM-1)属于

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免疫球蛋白超家族, 分布于纤维母细胞、血管内皮细胞和激活的淋巴细胞等表面。LFA-1和ICAM-1可提供协同刺激信号促进淋巴细胞活化、增殖和分化。在T细胞和抗原呈递细胞(antigen-presenting cells, APC)的相互作用中, LFA-1与ICAM-1配接, 直接参与启动免疫突触的形成。LFA-1还参与多种淋巴细胞的归巢过程。LFA-1与ICAM-1的相互作用也能介导一系列炎症反应[12]。大量的临床观察发现, LFA-1和ICAM-1的表达与风湿性关节炎、器官移植后的急性排斥反应、冠心病以及寻常型银屑病等许多疾病相关。

2 LFA-1与其配体的结合

目前, LFA-1已知的配体有ICAM-1、ICAM-2、ICAM-3和JAM-A等, 其中ICAM-1是其主要的配体。LFA-1与ICAM-1结合能力的调节主要有两种模式: LFA-1的亲和力(affinity)调节和LFA-1的亲合力(avidity)调节。在没有受到刺激时LFA-1处于弯曲构象(closed headpiece, bent), 即低亲和力构象, 此时LFA-1与ICAM-1等配体的结合能力很弱, 当遇到某种激活信号后, LFA-1膝盖部位完全伸展引起腿部结构域直立, LFA-1头部结构域远离细胞膜, LFA-1的αL和β2亚基的跨膜区以及胞内区彼此分开, LFA-1配体结合位点构象也发生相应的改变, 这时整合素LFA-1呈现高亲和力的伸展构象(open headpiece, extended)与配体以高亲和力结合[13-16](图1)。介于上述两种构象之间的中间亲和力构象被称为不完全伸展(closed headpiece, extended)的过渡态构象。LFA-1的亲合力调节是通过改变LFA-1在细胞表面的分布和聚集, 从而改变LFA-1对ICAM-l的结合效价而实现的。对于LFA-1与ICAM-1结合能力的这两种调节模式, Dustin等[17]认为, 首先LFA-1发生构象变化, 使个体LFA-1对ICAM-1亲和力增强, 然后通过胞内信号转导引起LFA-1聚集成簇, 导致在细胞接触位点亲合力增强。

3 LFA-1与ICAM-1的主要生理功能

3.1 LFA-1与ICAM-1的协同刺激信号和T淋巴细胞的活化

免疫活性细胞活化需要双信号刺激, 第二信号即协同刺激信号, 是APC表面协同刺激分子与淋巴细胞表面协同刺激分子受体结合、相互作用后产生的。

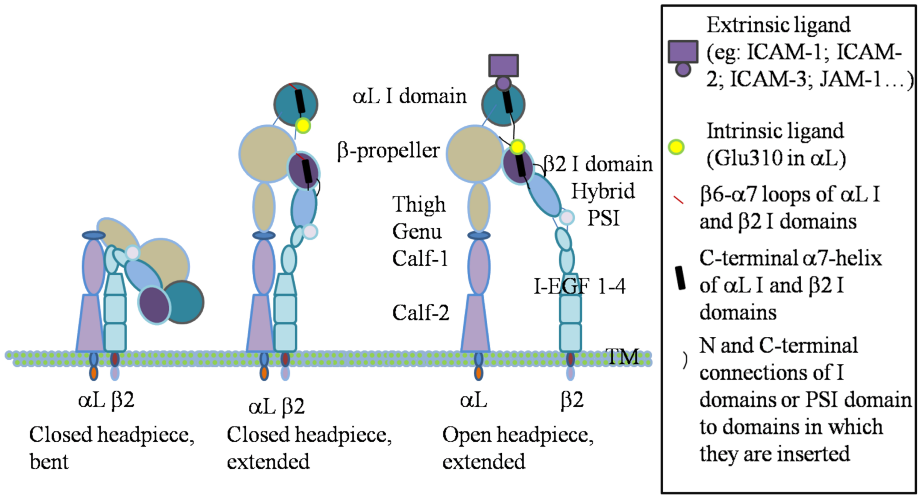
在T淋巴细胞活化过程中, 在不同抗原刺激的情况下, 在T细胞与APC的交界处, T细胞表面的LFA-1与APC表面的ICAM-1相互作用所传递的协同刺激信号可引起T淋巴细胞内肌动蛋白聚集成环状, 这种肌动蛋白环状聚集可降低T淋巴细胞活化的阈值从而促进T细胞活化。这种作用与胞内src激酶、SLP-76、ADAP和JNK的激活有关。体内外实验证明, 若APC缺乏ICAM-1将不能很好地使T细胞活化和增殖, 但可通过抗原剂量、外源性IL-2、其他协同刺激分子、增加反应T细胞密度来代偿, 而T细胞缺乏ICAM-1并没有相同的作用[18]。

通过对ICAM-1缺失的小鼠的研究发现, 用缺乏ICAM-1的APC刺激T细胞后, 静息细胞和记忆细胞比值没有明显变化, 但效应记忆细胞和中心记忆细胞的比值明显升高, 提示ICAM-1与LFA-1在T细胞分化为具有增殖能力的中心记忆细胞的过程中起重要作用[19]。

3.2 LFA-1与ICAM-1在免疫突触中的作用

T细胞免疫突触是T细胞与APC或靶细胞间形成的微结构域[20-21], 是T细胞活化的一种新的免疫协同刺激方式[22-23]。如图1显示, 免疫突触实际上是一个由突起的脂筏所形成的山丘, 有成熟型和非成熟型两种。Dustin等[24]证实了成熟型免疫突触的基本特征是APC与T细胞相互作用时TCR-MHC-抗原肽复合物(pMHC)位于中央区(直径1~3微米), 与Lck、ZAP-70和Fyn等信号分子一起被称为中央超级分子活化复合物(central supra-molecular activation cluster, cSMAC)。黏附分子ICAM-1-LFA-1与pMHC平行并围绕于其周围, 称为周边超级分子活化复合物(periphery supra-molecular activation cluster, pSMAC)(图2和图3)。

LFA-1与ICAM-1的结合直接参与启动免疫突触的形成, 免疫突触的形成包括三个阶段。第一阶段, 在T细胞受到刺激后, TCR/CD3转导的早期第一信号引起LFA-1对ICAM-1的亲和力及亲合力瞬时上调[25], Src激酶相关的磷蛋白SKAP-55进一步促进LFA-1与ICAM-1在T细胞与APC接触区域的相互作用[26]。LFA-1与ICAM-1配接, 启动T细胞与APC间的相互作用。ICAM-1在T细胞表面聚集成一个广泛的中央区, 此为支点, T细胞膜在其周围环绕形成环状结构。第二阶段, 发生在T细胞与APC接触5分钟后, LFA-1-ICAM-1信号随即引起T细胞肌动蛋白微丝和



在整合素LFA-1分子的激活过程中, LFA-1的构象由弯曲状态向伸展状态转化。表现为LFA-1头部的直立以及LFA-1的αL和β2两个亚基的胞内区和跨膜区的分离。

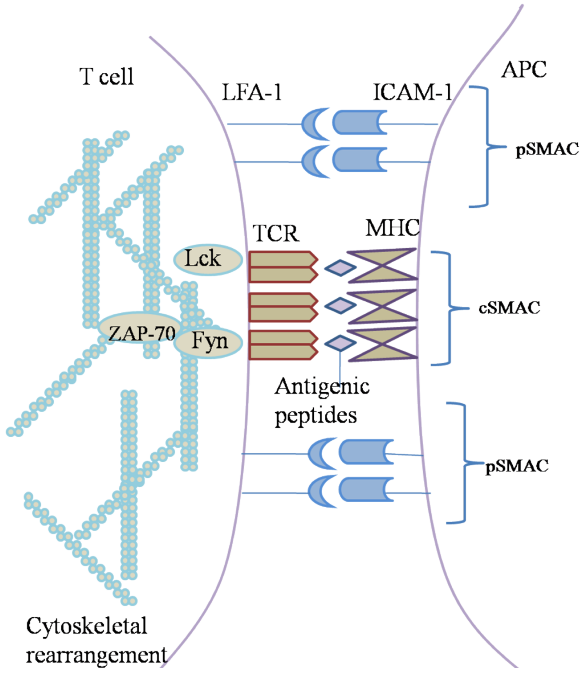
During the activation of the integrin LFA-1, the conformation of the LFA-1 changed from the bent state into the extended state. Including the upright of the head of LFA-1 and the separation of the intracellular region and the transmembrane region of αL and β2 subunits.

图1 整合素LFA-1亲和力(affinity)调节过程中的三种构象形式

Fig.1 Three conformational forms of integrin LFA-1 during its affinity regulation

肌动蛋白聚束表达水平增加而活化细胞骨架[27], 使依赖于PI-3K的T细胞微管组织中心重新定位和引发细胞膜上的不同分子发生转移, TCR-pMHC复合物向接触面的中心移动, 形成中央束, ICAM-1-LFA-1重新分布, 逐渐在外周形成一个环状结构(图3)。第三阶段, 中央束稳定化, 在细胞松弛素D的作用下, 中央束不再移动, T细胞迁移停滞而在T细胞与APC或靶细胞接触区域产生稳定的黏附复合体, 进而形成以TCR为中心的成熟的T细胞免疫突触。这种成熟的免疫突触可持续1小时以上。

在T细胞免疫突触的形成过程中, LFA-1-ICAM-1

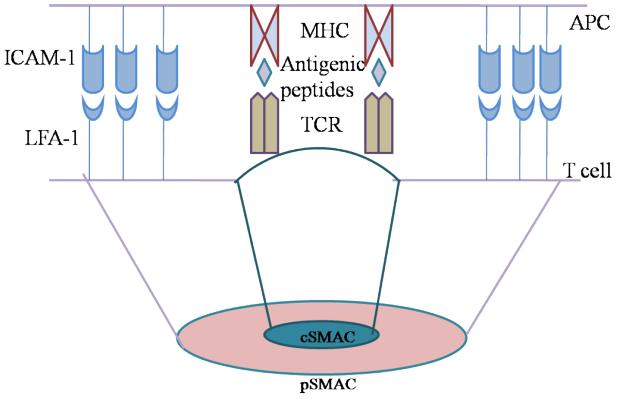


免疫突触是T细胞与APC相互作用的交界面, 图中显示cSMAC位于免疫突触中央而pSMAC位于外周。

The immune synapse is the interface of the interaction of T-cell and APC. The figure shows that the cSMAC is located in the center of the immunological synapse while the pSMAC is located in the outer circumference.

图2 免疫突触的纵切面

Fig.2 A longitudinal section of the immunological synapse

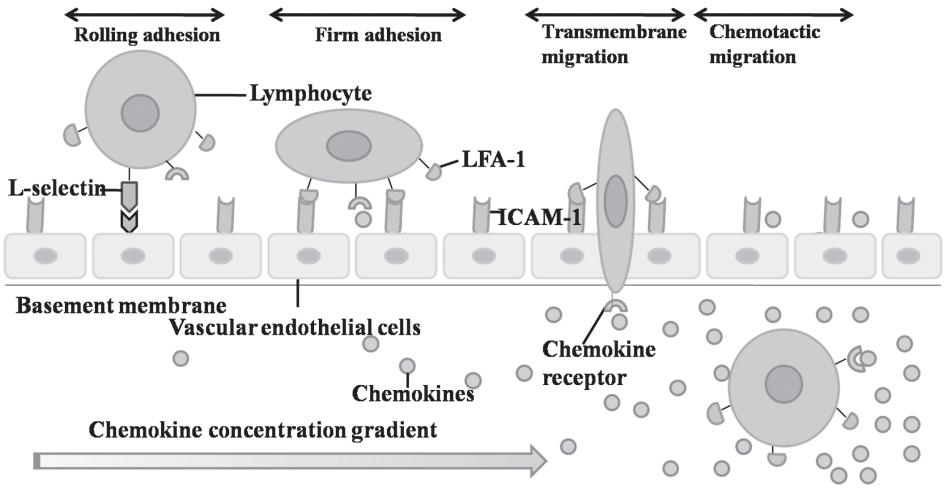


MHC-抗原肽-TCR等形成的cSMAC位于免疫突触中央区, ICAM-1-LFA-1形成环状结构围绕在cSMAC周围, 称为pSMAC。

sSMAC, which is composed of MHC-antigenic peptide-TCR is located in the immunological synapse central region, around it is a cyclic structure formed by ICAM-1-LFA-1, called pSMAC.

图3 免疫突触的立体示意图

Fig.3 A perspective schematic view of the immunological synapse



LFA-1与ICAM-1的结合使淋巴细胞从滚动黏附转为与内皮细胞的紧密结合, 并从内皮细胞间穿越血管内皮层及外侧的基底膜, 然后顺着趋化因子的浓度梯度向炎症部位迁移。

The binding of LFA-1 and ICAM-1 mediates lymphocytes from the rolling adhesion to firm adhesion to endothelial cells and induces lymphocytes passing through the blood vessels and the outside basement membrane, and then migrates to the inflammation sites along the concentration gradient of chemokines.

图4 LFA-1与ICAM-1的结合在淋巴细胞归巢中的作用

Fig.4 The role of the binding of LFA-1 and ICAM-1 in lymphocyte homing

复合体移向免疫突触外围形成外周超分子活化簇以维持免疫突触的稳定[20]。 这样, 在成熟的T细胞免疫突触中, LFA-1-ICAM-1复合体成为有效的屏障, 将大分子物质排除在免疫突触中心区域之外, 以避免大分子物质遮蔽TCR, 以及避免增大TCR与MHC-抗原多肽复合物的作用距离而影响T细胞的有效活化[22]。

3.3 LFA-1在淋巴细胞归巢中的作用

淋巴细胞归巢(lymphocyte homing)是淋巴细胞迁移的一种特殊形式, 血液中淋巴细胞选择性地穿越毛细血管后微静脉, 向对应器官或组织定向移动, 即为淋巴细胞归巢, 它包括淋巴细胞归巢至淋巴组织和非淋巴组织及向炎症部位的渗出等。归巢的分子基础是淋巴细胞与各组织、器官血管内皮细胞黏附分子的相互作用, 多种黏附分子与淋巴细胞的归巢有关。LFA-1是在淋巴细胞穿越血管内皮细胞的过程中起重要作用的一种黏附分子[28-30]。内皮细胞表达的趋化因子在选择性调节淋巴细胞归巢中有着重要作用, 它是通过吸引循环细胞以及激活整合素来发挥作用的[29,31-32]。如图3所示, 淋巴细胞贴壁后, 在L-选择素的介导下沿血管内皮缓缓滚动, 之后在LFA-1/ICAM-1等分子对的作用下, 与血管壁形成稳定黏附即捕捉。之后淋巴细胞主要由LFA-1/ICAM-1介导而向跨血管内皮迁移, 最后淋巴细胞穿过血管内皮细胞到达损伤部位。抗LFA-1的抗体对淋巴细胞从外周血向淋巴结的迁移可以有明显的干扰作用[33]。通过阻断LFA-1的功能, 可能引起了炎症组织附近的血管内皮细胞发生改变, 就不能刺激淋巴细胞穿过内皮细胞表面。与正常小鼠的行为相比, 在LFA-1缺乏的小鼠体内, 中性粒细胞和活化的T细胞都不能应答趋化因子梯度而穿越单层血管内皮细胞[34]。由此可见, LFA-1/ICAM-1在淋巴细胞归巢过程中起重要的作用。

4 LFA-1与ICAM-1和几种疾病的关系

4.1 LFA-1与类风湿性关节炎

类风湿性关节炎(rheumatoid arthritis, RA)是以损害滑膜、软骨和骨的一种慢性、炎性、系统性的自身免疫性疾病[35-36], 以慢性关节滑膜炎、关节损伤和骨破坏为特征。在关节发生炎性病变时, 在炎症的刺激下, 淋巴细胞及血管内皮细胞表面LFA-1和ICAM-1的表达明显增高。应用特异性抗体阻断LFA-1与ICAM-1的结合时, 可以降低关节炎的发病率以及疾病的严重程度, 证明LFA-1与ICAM-1的结合在关节炎的病程进展中起重要作用[37]。LFA-1可促进T细胞表面受体的活化从而使T细胞活化。一方面活化的T细胞受体发生交联, 其表面的LFA-1分子由低亲和力状态变为高亲和力状态, 与T细胞受体一起形成突触样环状结构, 促进T细胞的活化。活化的T细胞通过释放细胞因子及其他介质, 促进B细胞

活化形成浆细胞, 分泌大量的抗体, 分泌的抗体与抗原形成免疫复合物, 激活补体诱发炎症。另一方面, 在RA关节滑膜下有大量T淋巴细胞浸润和聚集, 它们与抗原提呈细胞相互作用, 产生细胞因子, 刺激细胞表面的黏附分子表达上调, 表达在细胞表面的各种黏附分子构成了关节和滑膜部位的免疫微环境。在关节滑膜部位的免疫微环境中, LFA-1分子在树突状细胞、淋巴细胞以及巨噬细胞表面均有表达, 其配体ICAM-1表达于血管的内皮细胞、树突状细胞以及活化的淋巴细胞和巨噬细胞表面。LFA-1通过与其配体ICAM-1结合, 促进炎症细胞之间的黏附及炎症细胞向局部的趋化反应, 从而促进疾病的发生、发展[38]。

4.2 LFA-1和其配体的结合与器官移植后急性排斥反应的关系

急性排斥反应是临床器官移植术后的主要并发症之一, 排斥反应会导致移植器官的功能恶化。寻找一种准确、及时的诊断急性排斥反应的方法, 对进一步提高器官移植术后存活率具有重要意义。LFA-1和ICAM-1的相互作用在急性排斥反应中起着重要的介导作用。目前, 已经有ICAM-1参与肾、肝等器官移植排斥反应的报道。

Teppo等[39]和Eriksson等[40]发现肾移植术后, sICAM-1在血和尿中的含量呈规律性变化。肾移植术后血和尿中sICAM-1的含量升高, 当发生排斥反应时, 血和尿中sICAM-1含量再次升高, 在排斥反应经治疗控制后, 血和尿中sICAM-1含量逐渐下降。在移植肾急性排斥反应过程中, LFA-1和ICAM-1参与了急性排斥反应的免疫反应和炎症反应的多个环节, 在白细胞黏附血管内皮细胞, 进而穿透肾血管内皮层浸润到移植肾组织的过程中起着非常重要的作用[41-42]。LFA-1和ICAM-1还能介导活化信号的传导, 为静止的T细胞活化提供协同刺激信号[43], 促进免疫效应细胞识别移植抗原, 启动排斥反应程序。这些机制可以导致移植肾的直接损伤。LFA-1和ICAM-1的结合还激活$CD8^+$ T细胞或自然杀伤细胞分化成为效应T细胞, 同时介导淋巴细胞与靶细胞的相互作用, 产生细胞介导的细胞溶解反应[44], 造成内皮细胞炎和肾小管炎, 导致移植肾功能丧失。

ICAM-1还介导APC与抗原特异性T细胞的相互作用以及细胞毒性T细胞和靶细胞的相互作用, 其表达水平一般与肝细胞损伤程度呈正比[45]。文献报道, 在肝移植发生急性排斥反应时, ICAM-1在窦内皮中表达增加并且可以表达于肝细胞中[46], 移植肝组织中ICAM-1和LFA-1的表达水平随急性排斥反应程度增强而明显增强。另有研究表明, 阻断LFA-1的结合位点可抑制移植排斥反应[47]。从机制上可解释为: 急性排斥反应主要由T淋巴细胞介导, 而ICAM-1与LFA-1的结合是启动T淋巴细胞黏附和活化的关键环节, T淋巴细胞活化后, 可对带有移植物抗原的靶细胞进行攻击, 导致急性排斥反应的程度增强。

由此可见, 在急性排斥反应时, 对组织中ICAM-1和LFA-1水平的检测可作为一种诊断移植急性排斥的方法, 对移植后急性排斥反应的诊断和治疗具有一定的参考价值。

4.3 ICAM-1与LFA-1在冠心病中的作用

冠状动脉性心脏病简称冠心病(coronary heart disease), 指由于脂质代谢不正常, 血液中的脂质沉着在原本光滑的动脉内膜上, 在动脉内膜一些类似粥样的脂类物质堆积而成白色斑块, 称为动脉粥样硬化病变。这些斑块渐渐增多造成动脉腔狭窄, 使血流受阻, 导致心脏缺血, 产生心绞痛。而研究发现, 在冠状动脉病变进展阶段, 在血清中可检测到ICAM-1水平增高[48], 在斑块处可以检测到单核细胞数量增多[49], ICAM-1水平及单核细胞数量越多者, 其冠脉病变程度越重。其机制可能是: 单核细胞上的LFA-1与内皮细胞上的ICAM-1在单核细胞与内皮细胞黏附过程中起到协同信号作用和激活多种促炎症信号级联反应[50]。同时, 激活状态的单核细胞可以增加两者的亲和力, 间接促进单核细胞的黏附, 单核细胞移行至血管内皮下, 引起血管平滑肌增生和泡沫细胞形成是最终导致粥样斑块形成的关键环节。血清中ICAM-1水平增高可作为冠状动脉粥样硬化严重性的标志[48], 也有国外学者尝试将LFA-1作为冠脉狭窄的预测指数, 但结果不一[51-52]。

4.4 LFA-1与银屑病

银屑病俗称牛皮癣(psoriasis), 是一种以表皮过度增生及炎性细胞(包括T淋巴细胞及中性粒细胞)浸润为特征的炎性皮肤病。

在银屑病的发病过程中伴随着LFA-1与ICAM-1的表达, 研究表明, 正常人皮肤ICAM-1及LFA-1阴性, 银屑病表皮角质形成细胞ICAM-1阴性, 而表皮和真皮内浸润细胞LFA-1阳性[53]。银屑病浸润的炎性细胞主要为记忆T细胞[54], 而该细胞可同

时表达ICAM-1和LFA-1, 因此银屑病皮损真皮内同一部位的炎性细胞可同时表达两种黏附分子。体外实验表明, ICAM-1可促进T淋巴细胞增殖[55], 因此我们见到真皮内炎性细胞ICAM-1表达强度与其数量呈显著正相关。另外, 炎性细胞尚可通过ICAM-1、LFA-1非依赖性机制向表皮内浸润[56], 如CD43/ICAM-1依赖性机制[57]。进行期寻常性银屑病皮损角质形成细胞和真皮内浸润炎性细胞表达CD43分子, 可与ICAM-1结合[58]。因此, 一方面表皮角质形成细胞上的ICAM-1可与真皮内炎性细胞上的CD43相互作用, 另一方面表皮角质形成细胞上的CD43分子可与真皮内炎性细胞上的ICAM-1相互作用, 从而促进炎性细胞浸润, 抗ICAM-1和抗LFA-1单抗不能完全抑制淋巴细胞等向表皮内迁移。

5 总结

综上所述, LFA-1和ICAM-1介导的信号转导在淋巴细胞迁移、黏附、活化和免疫突触形成中都有重要作用, 并可产生协同刺激信号影响淋巴细胞的增殖、分化和凋亡等, 与器官移植、感染和自身免疫疾病等密切相关。对LFA-1和ICAM-1的深入研究, 可以为临床治疗自身免疫疾病、器官移植和控制移植排斥等提供新的方法。

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