综述

成纤维细胞在糖尿病患者创伤愈合中作用的研究进展

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摘要 糖尿病患者皮肤易受损伤, 并因其复杂的异常病理生理学过程而愈合延迟或不愈合, 降低了患者的生活质量, 成为亟待解决的难点和热点。成纤维细胞(FB)是皮肤组织的重要细胞成分之一, 是真皮层中分泌细胞外基质(ECM)的主要修复细胞, 更是创伤愈合的关键与基础。近几年来, 有关糖尿病对FB的影响以及对其改变的研究发展迅速。最新研究发现, 糖尿病患者FB的改变在其创面难愈中起重要作用。该文就糖尿病创面愈合中糖尿病对FB的影响以及FB的变化作一综述, 以了解其具体机制。

关键词 糖尿病; 成纤维细胞; 创面愈合

Research Advances of Fibroblast in Diabetic Wound Healing

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Abstract Diabetic skin is vulnerable. The delayed healing results from its complicated abnormal pathophysiology process. The wound reduces the patient's quality of life and makes it becomes a difficult and hot pressing. Fibroblasts are one of the important components of skin tissue, the key and foundation to the wound healing as well. In recent years, the study of the effect of diabetes on fibroblasts and its changes is developing rapidly. It is found that the change of the diabetic fibroblasts in the wounds painless plays an important role. This paper reviewed the effect of diabetes on FB and the changes of FB in wound healing in order to understand its mechanism.

Keywords diabetes; fibroblast; wound healing

随着中国经济的迅速发展, 国民生活水平的提高, 饮食结构及快节奏等生活方式的改变, 糖尿病已经成为我国继肿瘤、心血管病变之后第三大严重威胁人类健康的慢性疾病。对于糖尿病患者来说, 在创面愈合延迟甚至不愈合中起重要作用的是成纤维细胞(FB)的改变[1-3]。研究表明糖尿病大鼠皮肤组织层次欠清晰, 部分表皮缺乏复层排列, 真皮层厚度明显变薄, 真皮层胶原排列紊乱, 部分胶原变形断裂[4]。FB是真皮层中分泌细胞外基质(ECM)的主要修复细胞, 有学者指出修复细胞数量上的平衡是维持皮肤

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组织正常代谢活动的基本条件, 是糖尿病皮肤容易发生自发溃疡和创面形成后难愈的基础[1,5-7]。因此, 糖尿病高糖状态影响了创面愈合, 参与了FB的运动。随着近年来分子生物学等学科的发展, 对创面愈合机制的研究也日趋深入。本文就糖尿病高糖状态下糖基化终末化产物(AGEs)、糖基化终末产物受体途径、FB数量减少、胶原蛋白减少、FBOS紊乱几个方面展开综述, 以探讨糖尿病高糖状态通过对FB的影响及改变而形成创伤难愈的现状。

1 糖尿病病理高糖状态产生AGEs

糖尿病患者因胰岛素绝对或相对不足, 导致血糖浓度长期处于高水平状态[8], 这种病理性高糖环境促进了蛋白质氨基与糖的醛基之间的非酶促糖基化反应[9], 形成晚期糖基化终末产物(AGEs)[10]。研究表明, 糖尿病大鼠机体内OS增强, 从而促进真皮基质中AGEs含量明显增高, 而AGEs蓄积又可导致OS增强, 形成一个恶性循环[11]。当AGEs蓄积到一定程度, 这个恶性循环可以不依赖高糖继续进行下去[12]。此外, 胶原糖基化后使FB生物学活动(如增殖、凋亡、迁移等)发生改变, 进一步引起ECM重塑被削弱或者受抑制[13-15]。研究证明, 不同浓度的AGEs对FB的生长均有一定的抑制作用, 且随着AGEs浓度的增高抑制作用更强[11]。真皮AGEs蓄积已被广泛认为是糖尿病创面不愈或延迟愈合的根本原因[15]。

2 AGEs受体调控FB生物学活动

AGEs通过非受体途径(如非酶性糖基化形成蛋白偶联)和受体途径(即通过与其细胞表面受体结合)影响病变的发生和发展[14], 其中受体途径是AGEs发挥生物学作用的主要途径[16]。已发现在人皮肤FB表面存在多种AGEs结合蛋白, 如P60、P90、dalectin-3及AGEs受体(RAGE)等[17]。和其他受体不同, RAGE并非清除体内的AGEs, 而是介导并放大细胞对AGEs的大部分应答反应[14]。长期的高糖环境使得参与创面愈合的组织细胞易于表达RAGE。AGEs与RAGE结合可引发细胞内OS、亚铁血红素加氧酶-1的表达和转录因子NF-κB的激活, 并可进一步增强RAGE的表达[18]。AGEs-RAGE的相互作用能阻止FB进入G_2/M期, 并促进FB凋亡[16]; AGEs-RAGE复合物可作用于FB, 减少纤维结缔组织和胶原组织生成, 抑制创面愈合[19]。抗体阻断AGEs-RAGE相互作用后, 基本可以消除糖基化基质对细胞增殖和凋亡的影响[19]。RAGE也可作为白细胞的黏附受体, 可溶性的AGEs与RAGE相互作用诱导炎症细胞移行, 固定的AGEs能局限炎症细胞并促其活化[20]。所以, 糖尿病状态下局部组织创伤后, 带有RAGE的FB使炎症细胞无法迅速趋化至损伤部位[21], 从而影响了正常创面愈合(图1)。

3 糖尿病病理高糖状态调控FB数量

FB是主要的修复细胞之一。FB活化成熟后分泌胶原、纤维连接蛋白等细胞外基质, 以填充组织缺损; 活化后的FB还通过分泌生长因子, 如转化生长因子-β(TGF-β), 参与创面愈合的调控[27]。近年来研究证明, 在一定浓度范围内, 血糖浓度和AGEs浓度越高, 对FB增殖抑制作用越明显。有研究发现, 烫伤后14天, 高糖大鼠皮肤创面的FB线粒体肿胀或空泡变性, 粗面内质网扩张, 部分可见散在核糖体、染色质边集, 出现许多空泡结构, 呈现典型的凋亡征象, 周围可见大量老化的纤维细胞[23-24]。Boor等[20]建立糖基化ECM模型模拟糖尿病患者的体内环境, 证实了FB分泌的ECM糖基化后可以抑制纤维细胞的黏附和增殖, 并导致凋亡细胞增多。细胞数量的平衡主要通过其增殖和凋亡过程实现, 因此糖尿病高糖状态下FB的减少将会严重影响创面愈合。

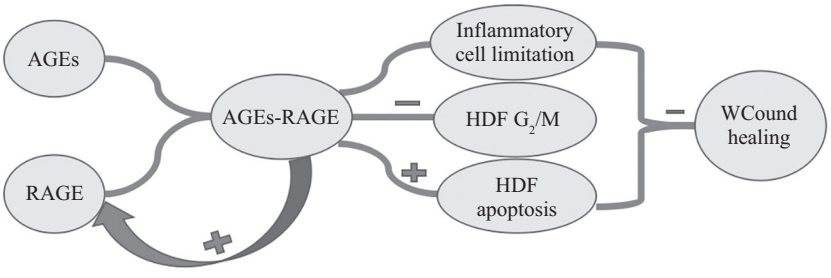

图1 AGEs受体调控机制模型

Fig.1 Receptor for AGEs regulatory mechanism model

4 糖尿病病理高糖状态影响FB调控胶原蛋白代谢

胶原代谢是一个多因素参与的复杂生物反应过程, 包括胶原合成和胶原分解[25]。皮肤胶原蛋白主要包括I型和III型胶原蛋白, 主要分布在皮肤真皮层, 由真皮FB合成[26]。前胶原是成熟胶原的前体分子, 它的水平可以反映胶原的生物合成活性。前胶原来源于FB, 因此皮肤中FB生成前胶原的功能决定了皮肤的弹性与强度, 所以FB数量和活性下降也可以导致胶原蛋白合成减少。糖尿病高糖状态下皮肤变薄的主要原因可能是胶原代谢过程的紊乱导致了胶原蛋白的减少[27]。研究显示, 高糖可抑制FB的I、III型前胶原蛋白mRNA的表达, 而I、III型前胶原mRNA表达活性的降低直接影响到I、III型胶原蛋白的含量, 导致FB分泌胶原蛋白明显减少[28]。金属蛋白酶(MMPs)是参与ECM降解的主要蛋白酶, 它受金属蛋白酶组织抑制物(TIMPs)的调控, MMPs和TIMPs的平衡是保证ECM重建的关键[29]。MMP-2由FB表达, 研究表明, 与正常组比较, 糖尿病高糖状态下*MMP-2*基因表达明显上调, 而*TIMP-2*基因表达下调, 呈现*MMP-2/TIMP-2*比值的明显升高[30]。

5 糖尿病病理高糖状态干扰FB的OS过程

氧化应激(OS)是指机体在遭受各种有害刺激时, 体内高活性分子如活性氧自由基(ROS)产生过多, 氧化程度超出氧化物的清除, 使氧化系统和抗氧化系统失衡, 从而导致组织损害, 对许多疾病的发展起着重要作用[31-32]。OS在糖尿病发病过程中为一原发且独立的参与因素。近年来的研究表明, OS在糖尿病皮肤创伤愈合中起了重要作用[33]。体内的氧化与还原反应在正常的生理状况下处于平衡状态, 活性氧及抗氧化系统是维持这一平衡状态的重要因素[34]。细胞OS途经相关指标包括丙二醛(MDA)、超氧化歧化酶(SOD)和谷胱甘肽(GSH)等。MDA作为衡量脂质过氧化程度的指标, 用来检测脂质过氧化物(LOOH)在细胞内的含量。SOD在机体氧化与抗氧化平衡中起重要作用, 是机体超氧阴离子自由基的清除剂, 能阻止并消除自由基的连锁反应, 保护机体免于伤害[35]。GSH是低分子清除剂, 它可清除过氧化氢(H_2O_2)、LOOH等, 是衡量机体抗氧化能力大小的重要因素。实验证实, 高糖状态刺激FB, 可以导致细胞的OS[36], 造成自由基增多, 抗氧化能力下降, 表现为SOD和GSH活力下降、MDA水平上升[37]。对于创面而言, 活性氧会抑制FB的迁移和增殖, 导致ECM合成减少[38-39]。Takahashi等[40]将创伤部位的FB单层培养, 并将其置于H_2O_2中, 发现这些创伤部位新形成的FB胞体内聚集了大量氧化剂并发生了凋亡, 证明OS诱导了因创伤刺激而增殖和迁移的FB凋亡[33]。因此, 糖尿病病理高糖状态下, 由于血液循环系统中OS水平的提高使FB发生以上病理过程, 从而影响了皮肤的创面愈合过程。

6 结语与展望

糖尿病患者延迟伤口愈合, 大量患者深受其害, 而其机制尚未清楚。本文总结了近年来的研究(表1), 发现糖尿病病理高糖状态产生AGEs, RAGE调控

表1 高糖状态下创面难愈的作用机制

Table 1 The mechanism of wound healing under the condition of high glucose

作用 Role	作用机制 Mechanism
Pathological hyperglycemia states produce AGEs[8]	Promote oxidative stress[9]; inhibition of FB growth[8]
RAGE regulate FB activity[15]	Mediating amplification of the cell response to AGEs[13]; prevent FB from entering G_2/M phase and promote FB apoptosis[9]; AGEs-RAGE reduces ECM generation[16]; glycosylated ECM inhibited FB adhesion and proliferation[23]
High glucose regulates the amount of FB[9,16]	Decrease in the number and activity of FB reduced its synthesis[24]; promote its apoptosis[20]
Disorder of collagen metabolism[25]	High glucose inhibits type I and III collagen secretion[26]; MMP-2/TIMP-2↑, degradation of the ECM↑[29]; high glucose stimulates FB, leading to oxidative stress of cells↑[36]
Interfering oxidative stress[31]	Reactive oxygen species cause FB migration and proliferation↓[38-39], apoptosis↑[33], ECM↓[12-14]

FB影响创面愈合, 调控FB数量影响创面愈合, 影响FB调控胶原蛋白代谢, 紊乱FB的OS过程。我们相信, 随着分子生物学等实验技术手段的不断提高, 糖尿病与FB之间相互作用的机制会越来越清晰, 从而为糖尿病难愈性创伤的预防和治疗提供新手段。

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