中国病理生理杂志 2008 24 (11): 2204-2208 ISSN: 1000-4718 CN: 44-1187/R

论著

MMP-9/TIMP-1表达在糖尿病鼠皮肤伤口愈合过程中的变化及意义初探

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收稿日期 2007-8-21 修回日期 2008-1-17 网络版发布日期 2009-2-8 接受日期 2008-1-17

摘要 目的：观察基质金属蛋白酶-9（MMP-9）、组织金属蛋白酶抑制剂-1（TIMP-1）的表达和MMP-9/TIMP-1比值在糖尿病组和正常组大鼠皮肤伤口愈合过程中不同时点表达的动态变化，探讨其可能的作用机制。

方法:糖尿病大鼠形成6周后行皮肤伤口造模，采用HE染色、Masson染色和免疫组织化学方法评估伤口形成后3、7、14 d伤口组织的再上皮化、炎症细胞浸润、肉芽组织厚度、新生血管形成和胶原纤维密度的情况；通过逆转录-聚合酶链反应(RT-PCR)和Western印迹检测术后不同时点MMP-9、TIMP-1在伤口组织中的表达情况。

结果:糖尿病大鼠伤口愈合明显迟缓。术后第3 d两组间胶原纤维、肉芽组织、新生血管和再上皮化没有差异，术后第7 d糖尿病组以上指标得分均低于正常组，第14 d这种趋势更加明显；而第3 d至14 d，糖尿病组的单核巨噬细胞浸润得分均低于正常组。术后第3 d两组MMP-9表达均达高峰，第7、14 d呈逐渐下降趋势，糖尿病组MMP-9表达水平在各时点均高于正常组；术后第3 d两组TIMP-1表达均达高峰，第7、14 d呈逐渐下降趋势，糖尿病组TIMP-1表达水平在各时点均低于正常组；正常组MMP-9/TIMP-1蛋白水平比值始终维持在一个动态平衡的稳定水平，而糖尿病组却长期处于高水平状态。

结论:异常的胶原产生、新生血管重建、炎症反应、再上皮化、肉芽形成可能是糖尿病鼠创面愈合减慢的组织病理学基础；皮肤组织MMP-9/TIMP-1的平衡性改变可能是这种组织病理学异常的重要原因之一。

关键词 糖尿病； 伤口愈合； 基质金属蛋白酶； 金属蛋白酶类组织抑制剂

分类号 R363

Imbalance between matrix metalloproteinases and tissue inhibitor of metalloproteinases during wound healing in diabetic rats

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Abstract

<FONT face=Verdana>AIM: To investigate the imbalance between the expression of metalloproteinases (MMPs) and that of tissue inhibitors of metalloproteinase (TIMPs) during wound healing in diabetic rats.
METHODS: Diabetic rats were induced with streptozotocin. All rats were maintained for 6 weeks. A full-thickness excisional wound was created on the back of each rat. Every group was randomly divided into 3 subgroups of 7 rats: 3 d group, 7 d group, 14 d group and animals were killed at 3rd, 7th and 14th day. Routine pathological examination, Masson′s trichrome staining and immunohistochemistry were made to calculate the score of epidermal and dermal regeneration, granulation tissue thickness, angiogenesis, matrix density, and infiltrated cells at different time points. RT-PCR and Western blotting were used to detect the expression of mRNA and protein of MMP-9 and TIMP-1 in the skin at those time points.
RESULTS: Six weeks after streptozotocin treatment, Three days after injury, the wound healing rate of normal rats was faster than that of diabetic rats. From 3rd to 14th day, there were a lot of fibroblast and macrophage in normal skin, while few such cells were observed in diabetic skin. The other histological scores in normal skin were higher than those in diabetic rats at 7th and 14th day. Both MMP-9 and TIMP-1 had minimally detectable

levels before wounding but exhibited rapid, significantly large increases within 3 d after wounding. Subsequently, they showed a rapid decline by 14 d. The relative values of expression of MMP-9 mRNA and protein in diabetic group were higher than those in normal group at different time points. However, the values of TIMP-1 mRNA and protein in diabetic group were significantly lower than those in control group. Significant difference was observed between two groups with the ratio of MMP-9/TIMP-1, higher in diabetic group than that in normal group.
CONCLUSION: Abnormal reepithelialization, angiogenesis, inflammatory cell infiltration, collagen fibers generation, granulation tissue deposition, seem to be the basic histopathology that delays wound healing. The imbalance between MMPs and TIMPs in diabetic skin tissue before and after injury may be one of the important reasons of these alterations of histopathology.</FONT>

Key words Diabetes mellitus Wound healing Matrix metalloproteinases Tissue-inhibitor of metalloproteinases

DOI: 1000-4718

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