New Day in Medicine
Новый День в Медицине
NDM

TIBBIYOTDA YANGI KUN

Ilmiy referativ, marifiy-ma'naviy jurnal

AVICENNA-MED.UZ

ISSN 2181-712X.
EiSSN 2181-2187

4 (54) 2023

www.bsmi.uz
https://newdaymedicine.com
E: ndmuz@mail.ru
Тел: +99890 8061882

ТИББИЁТДА ЯНГИ КУН
НОВЫЙ ДЕНЬ В МЕДИЦИНЕ
NEW DAY IN MEDICINE

Илмий-рефератив, маънавий-маърифий журнал
Научно-реферативный,
духовно-просветительский журнал

УЧРЕДИТЕЛИ:

БУХАРСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ ИНСТИТУТ
ООО «ТИББИЁТДА ЯНГИ КУН»

Национальный медицинский исследовательский центр хирургии имени А.В. Вишневского является генеральным научно-практическим консультантом редакции

Журнал был включен в список журнальных изданий, рецензируемых Высшей Аттестационной Комиссией Республики Узбекистан (Протокол № 201/03 от 30.12.2013 г.)

4 (54)

2023

апрель

Received: 20.04.2023, Accepted: 25.04.2023, Published: 29.04.2023.

UDC 616-001.4-002.3-08

THE ROLE OF CHANGES IN THE CONTENT OF PROTEASES AND PROTEASE INHIBITORS IN CHRONIC PURULENT WOUNDS

Mirzaev K.K., Azizov D.T.

Andijan State Medical Institute, 170100, Uzbekistan, Andijan, Atabekova st.1 Тел:(0-374)223-94-60. E-mail: info@adti

✓ ***Resume***

The work studied the features of changes in the content of proteases and protease inhibitors in chronic purulent wounds. It was concluded that in postoperative wounds, the indicators of general proteolytic activity and antiproteolytic activity do not differ significantly; there is a balance between proteases and protease inhibitors, which presumably can be regulated by local mechanisms. In chronic purulent wounds, the total proteolytic activity is significantly higher than that of postoperative wounds. At the same time, the antiproteolytic activity is significantly lower than the total proteolytic activity, and also lower than the antiproteolytic activity of postoperative wounds, which creates a pronounced imbalance between proteases and protease inhibitors and contributes to the chronicity of the inflammatory process in purulent wounds with the involvement of both local and systemic mechanisms of regulation.

Keywords: proteases, protease inhibitors, postoperative wounds, chronic purulent wounds, proteolytic activity, antiproteolytic activity.

РОЛЬ ИЗМЕНЕНИЯ СОДЕРЖАНИЯ ПРОТЕАЗ И ИНГИБИТОРОВ ПРОТЕАЗ ПРИ ХРОНИЧЕСКИХ ГНОЙНЫХ РАНАХ

Мирзаев К.К., Азизов Д.Т.

Андижанский государственный медицинский институт, 170100, Узбекистан, г. Андижан, ул. Атабекова, 1 Тел:(0-374)223-94-60. E.mail: info@adti

✓ ***Резюме***

В работе изучены особенности изменения содержания протеаз и ингибиторов протеаз при хронических гнойных ранах. Сделан вывод, что в послеоперационных ранах показатели общей протеолитической активности и антипротеолитической активности достоверно не различаются; существует баланс между протеазами и ингибиторами протеаз, который предположительно может регулироваться локальными механизмами. При хронических гнойных ранах общая протеолитическая активность значительно выше, чем при послеоперационных ранах. При этом антипротеолитическая активность значительно ниже общей протеолитической активности, а также ниже антипротеолитической активности послеоперационных ран, что создает выраженный дисбаланс между протеазами и ингибиторами протеаз и способствует хронизации воспалительного процесса в гнойных ранах. с участием как местных, так и системных механизмов регуляции.

Ключевые слова: протеазы, ингибиторы протеаз, послеоперационные раны, хронические гнойные раны, протеолитическая активность, антипротеолитическая активность.

SURUNKALI YIRINGLI YARALARDA PROTEAZALAR VA PROTEAZA INGIBITORLARI MAZMUNINI O‘ZGARISHINING O‘RNI

Mirzaev K.K., Azizov D.T.

Andijon davlat tibbiyot instituti O'zbekiston, Andijon, Otabekov 1 Tel: (0-374) 223-94-60. E.mail: info@adti

✓ ***Rezyume***

Ishda surunkali yiringli yaralarda proteazlar va proteaz inhibitörleri tarkibidagi o'zgarishlarning xususiyatlari o'rganildi. Operatsiyadan keyingi jarohatlarda umumiy proteolitik faollik va antiproteolitik faollik ko'rsatkichlari sezilarli darajada farq qilmaydi, degan xulosaga keldi; proteazlar va proteaz inhibitörleri o'rtasida mutanosiblik mavjud bo'lib, ular ehtimol mahalliy mexanizmlar bilan tartibga solinishi mumkin. Surunkali yiringli yaralarda umumiy proteolitik faollik operatsiyadan keyingi jarohatlarga qaraganda ancha yuqori. Shu bilan birga, antiproteolitik faollik umumiy proteolitik faollikdan sezilarli darajada past, shuningdek operatsiyadan keyingi yaralarning antiproteolitik faolligidan past bo'lib, bu proteazlar va proteaz inhibitörleri o'rtasida aniq nomutanosiblikni keltirib chiqaradi va yiringli yaralarda yallig'lanish jarayonining surunkali bo'lishiga yordam beradi. tartibga solishning ham mahalliy, ham tizimli mexanizmlarini jalb qilish bilan.

Kalit so'zlar: proteazlar, proteaz inhibitörleri, operatsiyadan keyingi yaralar, surunkali yiringli yaralar, proteolitik faollik, antiproteolitik faollik.

Relevance

In addition to clinical signs of infection (eg, inflammation, pus, and pain), microbial counts have historically been used to determine wound infection. However, it is increasingly recognized that not only is high bioburden detrimental to wound healing, but that the virulence of the invading microorganism and the immune status of the host may influence clinical outcomes. Bacteria such as Pseudomonas aeruginosa, Staphylococcus aureus, and Staphylococcus epidermidis have developed a number of virulence factors that help them overcome host defenses and multiply in underlying soft tissues. More specifically, bacterial proteases are one such virulence factor that is involved in promoting invasion and destruction of host tissue. Due to the complexity of microorganisms, proteases can negatively impact the wound environment, resulting in delayed wound healing. The data obtained indicate that proteases can play an important role in wound infections, promote the development of an inflammatory response and interfere with wound healing [11].

Bacterial proteases contribute to the induction of an inflammatory response in the host. Proteases produced by bacteria have been found to activate the kinin system and degrade kininogens, which subsequently causes an inflammatory response in the form of edema, redness, and pain [9].Like other immunological factors, bacterial proteases can also interfere with phagocytosis [7], reduce leukocyte activity [6], inhibit neutrophil function, and prevent chemotaxis [8] .

Bacterial proteases can degrade a number of biologically important host proteins, such as complement components C3 and C1q [4], and prevent the formation of C5 by destroying C3 [10]. Due to this, the opsonization and phagocytosis of neutrophils is disturbed, hindered or even prevented [15].

The function of bacterial proteases in overcoming the host's immune system is to degrade the host's immunoglobulin [16]. This can be particularly detrimental to the host given the role of immunoglobulins in recognizing and helping to neutralize invading microorganisms. Various researchers have reported the effect of proteases on the degradation of immunoglobulins, including immunoglobulin A (IgA) and immunoglobulin G (IgG) [4].

Proteases and their inhibitors contribute to the balance between degradation and deposition of the extracellular matrix (ECM), creating a balance necessary for the timely and coordinated healing of skin wounds. However, when this balance is disturbed, wounds become chronic, characterized by abundant levels of proteases and reduced levels of protease inhibitors [13].

The ratios of proteases and their inhibitors have also been used as predictive markers of wound progression to healing [14].

Many researchers emphasize the key role of proteases in wound healing. Therefore, it is necessary to control the expression of proteases in the wound environment and the ways in which overexpression and activation of proteases can lead to a delay in the healing process of skin wounds. Future research should aim to explore ways in which proteases can be targeted as an alternative therapeutic approach to wound management, and to assess the advantages and disadvantages of using wound fluids to evaluate wound progression in terms of proteolytic activity [13].

Materials and methods

In the work, 12 patients with postoperative wounds (control) were examined in the first group and 15 patients with purulent wounds in the second group (experiment). All patients in the diagnosis were absent of cardiovascular diseases, diabetes and metabolic changes. The material for the study was obtained by collecting swabs with sterile saline from the surface of postoperative and purulent wounds.

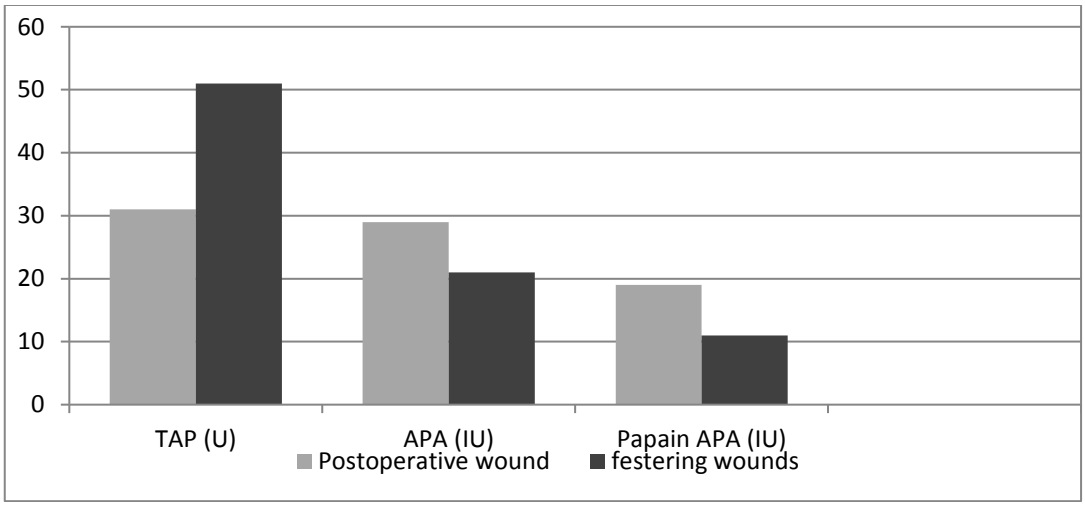
The total proteolytic activity in the washing composition was determined by the caseinolytic method by accounting for the products of casein hydrolysis in units of activity (U) for tyrosine. The inhibitory (anti-proteolytic) activity of the obtained swabs was determined by the caseinolytic test, according to the ability to decrease the activity of 0.01% trypsin and 0.01% papain, when they were incubated with the studied samples of swabs compared with samples of swabs with trypsin or papain without incubation. The inhibitory activity was expressed in inhibitory units [13].

For the purpose of the severity of proteolysis in wounds, the proteolysis index was calculated - the ratio of proteolytic activity to antiproteolytic activity (OPA/APA).

The data obtained were subjected to statistical processing using standard Microsoft Excel 2007 programs with the calculation of average values (M), their errors (m), and the coefficient of significance of the difference between average Student-Fisher values (t).

Results and discussion

The data obtained showed (Fig.) that in patients with postoperative wounds, the average PSA in the wash composition was 31.7±2.8 U/ml. At the same time, in patients with purulent wounds, this indicator was significantly higher compared with similar results of postoperative wounds, and amounted to 52.4±4.8 U/ml (P<0.01).



Picture. *Changes in the indicators of total proteolytic activity (TPA) and antiproteolytic activity (APA) of washings of postoperative and purulent wounds.*

** - Significantly different values relative to the parameters of the TPA of purulent wounds.*

O - significantly different values relative to the corresponding indicators of the OPA of postoperative wounds.

At the same time, the indicator of antiproteolytic activity for trypsin in the composition of washings of postoperative wounds was 28.9 ± 2.5 IU/ml, which was not significantly lower than the TPA in the washings of postoperative wounds, and the proteolysis index of TPA / APA for trypsin was also not significantly higher and equal to 1.1 ± 0 ,one. In patients with purulent wounds, the index of antiproteolytic activity for trypsin was significantly lower compared to similar results in patients with postoperative wounds and amounted to 21.2±1.9 IU/ml (P<0.05), and also significantly lower than the TPA of purulent washings. wounds. Taking these data into account, the TPA /APA proteolysis index for trypsin was at the level of 2.5±0.22, which was significantly higher than the same indicator in the composition of postoperative wound lavages. The result of antiproteolytic activity for papain in the composition of washings of postoperative wounds was 19.1±1.5 IU/ml, this indicator was significantly less than the antiproteolytic activity for trypsin, due to the lower content of protease inhibitors that

bind to papain. For the same reason, the papain proteolysis index of TPA/APA increased and was equal to 2.7±0.24.At the same time, in patients with purulent wounds, the antiproteolytic activity for papain was also significantly lower than the antiproteolytic activity for trypsin and amounted to 11.6 ± 0.9 IU / ml ($P < 0.05$), this also manifests itself with a lower content of protease-binding inhibitors. with papa. At the same time, the proteolysis index of TPA /APA in the study of purulent wounds by papain was equal to 4.5, which was higher than the proteolysis index of postoperative wounds.

It is assumed that trypsin-like serine proteases in the wound environment bind mainly to two inhibitors of a1-proteinase inhibitor (a1IP) and a2-macroglobulin (a2M) in a fundamentally different way. The former completely inactivates the catalytic function of proteases, while the latter only limits their ability to cleave most high molecular weight substrates. In addition, the rate constant of the reaction of such proteases with a2M is 6 times higher than that with a1IP, thus forming an active complex capable of hydrolyzing specific substrates, which allows most of the enzymes entering the wound environment to bind to a2M. It should be emphasized that cysteine proteinases (papain), in contrast to serine proteases, bind mainly to a2M, and a1IP does not play a significant role in blocking the activity of proteinases. These data led to the conclusion that serine and cysteine proteinases can perform their function in the a2M-bound state [1].The inhibitory ability of trypsin can be manifested significantly due to low molecular weight inhibitors present in the composition of the wound wash and alpha-1-antitrypsin, and the inhibitory ability of papain due to high-molecular inhibitors of alpha-1-antitrypsin and alpha 2-macroglobulin. Considering that the low molecular weight inhibitor present in the composition of the wound lavage may be a secretory leukocyte protease inhibitor, which locally provides protection and has a pronounced anti-inflammatory, antibacterial and antifungal activity. Then, the decrease in trypsin inhibitory activity in the washout with pronounced manifestations of inflammation can be explained as a pronounced pro-inflammatory and microbial reaction, which is also manifested by an increase in TPA due to a decrease in this inhibitor. An increase in TPA in the composition of wound washings is also possibly associated with an increase in the functional activity of protease-producing cells due to a chronic inflammatory process [2,3].

As for the inhibitory ability of papain due to high-molecular inhibitors in the composition of wound washings, the main high-molecular papain inhibitors can be alpha-1-antitrypsin and alpha-2-macroglobulin, which are produced by the liver and have an inhibitory effect on proteases in all organs and tissues of the body [2,3]. Therefore, a decrease in the inhibitory ability of papain in the composition of wound washings can be regarded as a systemic manifestation of inflammation or, possibly, the degree of chronicity of the inflammatory process.

Based on this, our data on antiproteolytic activity for papain and trypsin can be interpreted as follows. In postoperative wounds, without pronounced manifestations of inflammation, there is a balance between proteases and protease inhibitors, which are regulated to a greater extent by local mechanisms. At the same time, in chronic purulent wounds with a pronounced inflammatory process, the balance between proteases and protease inhibitors is disturbed due to the disruption of local and systemic mechanisms.

Conclusions

In postoperative wounds, indicators of total proteolytic activity and antiproteolytic activity do not differ significantly, there is a balance between proteases and protease inhibitors, which presumably can be regulated by local mechanisms. In chronic purulent wounds, the total proteolytic activity is significantly higher than that of postoperative wounds. At the same time, the antiproteolytic activity is significantly lower than the total proteolytic activity, and also lower than the antiproteolytic activity of postoperative wounds, which creates a pronounced imbalance between proteases and protease inhibitors and contributes to the chronicity of the inflammatory process in purulent wounds with the involvement of both local and systemic mechanisms of regulation.

LIST OF REFERENCES:

1. Veremeenko K.N., Kizim A.I., Dosenko V.E. a 2-macroglobulin: structure, physiological role and clinical significance // Lab. Diagnostics. 2000;2:3-9.
2. Kolesnikova E.V. Alpha-1-antitrypsin deficiency: a modern view of the problem // Modern gastroenterology. 2008;2(40):93-98.
3. Doumas S., Kolokotronis A., Stefanopoulos P. Anti-inflammatory and antimicrobial roles of

secretory leukocyte protease inhibitor // Infection and immunity. 2005;73(3):1271-1274.
4. Engel LS, Hill JM, Caballero AR, Green LC, O'Callaghan RJ. Protease IV, a unique extracellular protease and virulence factor from Pseudomonas aeruginosa. // Journal of Biological Chemistry. 1998 Jul 3;273(27):16792-7.
5. Engel LS, Hill JM, Moreau JM, Green LC, Hobden JA, O'Callaghan RJ. Pseudomonas aeruginosa protease IV produces corneal damage and contributes to bacterial virulence. Investigative ophthalmology & visual science. 1998 Mar 1;39(3):662-5.
6. Hoge R, Pelzer A, Rosenau F, Wilhelm S. Weapons of a pathogen: proteases and their role in virulence of Pseudomonas aeruginosa. Current research, technology and education topics in applied microbiology and microbial biotechnology. 2010;2:383-95.
7. Kharazmi A, Eriksen HO, Döring G, Goldstein W, Høiby N. Effect of Pseudomonas aeruginosa proteases on human leukocyte phagocytosis and bactericidal activity. Acta Pathologica Microbiologica Scandinavica Series C: Immunology. 1986 Nov;94(1- 6):175-9.
8. Kharazmi A, Høiby N, Döring G, Valerius NH. Pseudomonas aeruginosa exoproteases inhibit human neutrophil chemiluminescence. Infection and immunity. 1984 Jun 1;44(3):587-91.
9. Koziel J, Potempa J. Protease-armed bacteria in the skin. Cell and tissue research. 2013 Feb;351(2):325-37.
10. Kuo CF, Lin YS, Chuang WJ, Wu JJ, Tsao N. Degradation of complement 3 by streptococcal pyrogenic exotoxin B inhibits complement activation and neutrophil opsonophagocytosis. Infection and immunity. 2008 Mar 1;76(3):1163-9.
11. Lindsay S., Oates A., Bourdillon K. The detrimental impact of extracellular bacterial proteases on wound healing // International wound journal. 2017;14(6):1237-1247.
12. McCarty S.M., Percival S.L. Proteases and delayed wound healing // Advances in wound care. 2013;2(8):438-447.
13. McCarty S. M., Percival S. L. Proteases and delayed wound healing //Advances in wound care. 2013;2(8):438-447.
14. Muller M., Trocme C., Lardy B., Morel F., Halimi S., Benhamou P.Y. Matrix metalloproteinases and diabetic foot ulcers: the ratio of MMP- 1 to TIMP- 1 is a predictor of wound healing // Diabetic Medicine. 2008;25(4):419-426.
15. Potempa J, Pike RN. Corruption of innate immunity by bacterial proteases. // Journal of innate immunity. 2009;1(2):70-87.
16. Schmidtchen A, Wolff H, Hansson C. Differential proteinase expression by Pseudomonas aeruginosa derived from chronic leg ulcers. // Acta Dermatovenereologica-Stockholm -. 2001 Nov 1;81(6):406-9.

Entered 20.04.2023