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Proteolytic homeostasis in skin following experimental cutaneous wounding in rats with monosodium glutamate-induced obesity

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Background. Obesity contributes to the pathogenesis of numerous skin diseases and impairs wound healing by disrupting extracellular matrix homeostasis and tissue remodeling. However, the state of the skin proteolytic system following wound healing under obese conditions remains poorly understood. This study aimed to evaluate alterations in the skin proteolytic system following wound healing in rats with and without monosodium glutamate-induced (MGI) obesity.

Materials and methods. Forty male outbred rats were divided into four groups (n = 10): Intact control, MGI obesity (MGI-Ob), Wound, and MGI-Ob + Wound. Full-thickness excisional skin wounds were created in the Wound and MGI-Ob + Wound groups. Following complete macroscopic wound closure, skin samples were collected from the healed wound site. Total proteolytic activity and enzymatic activities of metal-dependent and serine proteases were determined using selective inhibition. Gelatin zymography was performed to characterize qualitative changes in the gelatinolytic protease profile.

Results. Total proteolytic activity progressively increased in animals of all experimental groups, reaching the highest level in rats with MGI obesity following experimental wound healing. Serine proteases contributed more substantially to the overall increase in proteolytic activity than metal-dependent proteases. Gelatin zymography revealed progressive remodeling of the gelatinolytic protease profile, characterized by a shift from the predominance of putative active MMP-13 in intact control rats to low-molecular-weight gelatinolytic fragments following wound healing under obese conditions.

Conclusion. Experimental obesity was associated with persistent activation of the skin proteolytic system and qualitative remodeling of the gelatinolytic protease profile following wound closure, indicating dysregulation of proteolytic homeostasis during the late phase of wound healing.

Key words: obesity, cutaneous wound healing, proteolytic homeostasis, proteolytic activity, serine proteases, metal-dependent proteases, matrix metalloproteinases, gelatin zymography, skin, rats.

Протеолітичний гомеостаз шкіри за експериментального моделювання ран у щурів із глутамат-індукованим ожирінням

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Актуальність. Ожиріння сприяє розвитку численних захворювань шкіри та порушує процеси загоєння ран, змінюючи гомеостаз позаклітинного матриксу та процеси ремоделювання тканин. Водночас стан протеолітичної системи шкіри після загоєння ран за ожиріння залишається недостатньо вивченим. Метою дослідження було оцінити зміни протеолітичної системи шкіри після загоєння ран у щурів за наявності та відсутності глутамат-індукованого (ГІО) ожиріння.

Матеріали та методи. Дослідження проведено на 40 нелінійних самцях щурів, яких було розподілено на чотири групи ($n = 10$): інтактний контроль, тварини з глутамат-індукованим ожирінням (MGI-Ob), тварини з експериментальною раною (Wound) і тварини з глутамат-індукованим ожирінням та експериментальною раною (MGI-Ob + Wound). У тварин груп Wound та MGI-Ob + Wound моделювали повношарову ексцизійну рану шкіри. Після повного макроскопічного закриття рани відбирали зразки шкіри з ділянки загоєної рани. Загальну протеолітичну активність, а також активність металозалежних і серинових протеаз визначали за допомогою селективних інгібіторів. Для оцінки якісних змін профілю желатинолітичних протеаз проведено желатинову зимографію.

Результати. Загальна протеолітична активність поступово зростала у тварин усіх експериментальних груп і досягала максимального рівня у щурів із ГІО після загоєння експериментальної рани. Серинові протеази забезпечували більш вагомий внесок у загальне підвищення протеолітичної активності, ніж металозалежні протеази. Желатинова зимографія виявила прогресуюче ремоделювання профілю желатинолітичних протеаз, що характеризується перерозподілом від домінування ймовірно активної MMP-13 у гомогенатах шкіри інтактних щурів до переважання низькомолекулярних желатинолітичних фрагментів після загоєння ран за ожиріння.

Висновки. Експериментальне ожиріння асоціювалося зі стійкою активацією протеолітичної системи шкіри та якісним ремоделюванням профілю желатинолітичних протеаз після загоєння рани, що могло свідчити про порушення протеолітичного гомеостазу на більш віддалених етапах репарації шкіри.

Ключові слова: ожиріння, загоєння шкірних ран, протеолітичний гомеостаз, протеолітична активність, серинові протеази, металозалежні протеази, матриксні металопротеїнази, желатинова зимографія, шкіра, щури.

Obesity has become one of the most significant public health challenges worldwide because of its increasing prevalence and association with numerous chronic diseases [1–3]. Beyond its well-established metabolic and cardiovascular consequences, obesity profoundly affects skin structure and function by disrupting extracellular matrix (ECM) homeostasis, promoting chronic low-grade inflammation, and impairing tissue repair processes [4–6]. Accumulating

evidence suggests that obesity impairs cutaneous wound healing; however, the molecular mechanisms underlying obesity-associated alterations in skin repair remain incompletely understood [7, 8].

Proteolytic enzymes are key regulators of ECM turnover and tissue remodeling during cutaneous wound healing. By degrading ECM components and activating growth factors, cytokines, and other bioactive mediators, proteolytic cascades regulate cell migration, angiogenesis, and tissue remodeling required for successful tissue repair [9, 10]. Among these enzymes, matrix metalloproteinases (MMPs) and serine proteases represent the major proteolytic systems responsible for maintaining the balance between ECM degradation and synthesis, which is essential for restoring normal tissue architecture [11, 12]. Dysregulation of these proteolytic systems may result in excessive ECM degradation, persistent matrix remodeling, and impaired wound healing. The aim of this study was to evaluate alterations in the skin proteolytic system following wound healing in rats with and without monosodium glutamate-induced (MGI) obesity.

Material and methods. Ethics approval. All experimental procedures involving animals were conducted in accordance with the *European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes* (Strasbourg, 1986) and the Law of Ukraine «On the Protection of Animals from Cruelty». The study protocol was approved by the Bioethics Committee of the Educational and Scientific Centre «Institute of Biology and Medicine», Taras Shevchenko National University of Kyiv (*Protocol No. 4, approved 30.07.2024*). Throughout the study, animals were housed under standard laboratory conditions ($22 \pm 3^\circ\text{C}$, relative humidity $60 \pm 5\%$, 12 h light/12 h dark cycle) with free access to standard laboratory chow and water.

Experimental design. The study was performed using 40 male outbred white rats derived from eight litters born within a 1–2-day interval. Animals were randomly allocated to four experimental groups ($n = 10$ per group): (1) Intact control – healthy animals without obesity induction or cutaneous wounding; (2) MGI-Ob – rats with monosodium glutamate-induced obesity; (3) Wound – healthy rats subjected to full-thickness excisional skin wounding; and (4) MGI-Ob + Wound – rats with monosodium glutamate-induced obesity subjected to full-thickness excisional skin wounding.

Experimental obesity was induced by subcutaneous administration of monosodium glutamate ($4.0\text{ mg} \cdot \text{kg}^{-1}$ body weight) on postnatal days 2, 4, 6, 8, and 10 [13]. Control animals received equivalent volumes of physiological saline following the same schedule.

At four months of age, rats in the Wound and MGI-Ob + Wound groups underwent creation of a full-thickness excisional wound ($1 \times 1\text{ cm}$) on the dorsal skin under general anesthesia induced with thiopental sodium ($60\text{ mg} \cdot \text{kg}^{-1}$ body weight; Biochemie GmbH, Austria). Wounds were created using sterile surgical scissors and forceps and were left untreated throughout the experimental period.

Following complete wound closure (24 days after wound creation), animals were weighed and euthanized under ether anesthesia. Body weight, naso-anal length, and visceral adipose tissue mass were recorded. Obesity was confirmed using the Lee index, calculated as the cube root of body weight (g) divided by the naso-anal length (cm). Animals with a Lee index ≥ 0.30 were classified as obese, whereas those with a Lee index < 0.30 were considered non-obese [14].

Skin specimens were collected from the healed wound site (scar tissue) in wounded animals and from the corresponding dorsal skin region in intact controls animals. Tissue samples were homogenized on ice in physiological saline and filtered through four layers of nylon mesh. The homogenates were used for all subsequent biochemical analyses.

Determination of total proteolytic activity and the activities of metal-dependent and serine proteases. Total proteolytic activity in skin homog-

enates was determined using casein as a substrate according to the method [15] with minor modifications. Aliquots containing 50 µg of total protein were incubated with 2 % casein prepared in 50 mM Tris-HCl buffer (pH 7.4) containing 0.13 M NaCl at 37 °C for 30 min. The reaction was terminated by adding trichloroacetic acid to a final concentration of 7 %, followed by incubation at 4 °C for 15 min and centrifugation at 15,000 × g for 30 min. The absorbance of the resulting supernatant was measured at 280 nm using a SmartSpec Plus spectrophotometer (Bio-Rad, Hercules, CA, USA). Reaction mixtures in which tissue homogenates were replaced with an equivalent volume of Tris-HCl buffer served as blank. Total proteolytic activity was expressed as relative units per milligram of total protein (rel. Units × mg⁻¹ protein).

The activities of metal-dependent and serine proteases were determined using selective inhibition with ethylenediaminetetraacetic acid (EDTA) and phenylmethylsulfonyl fluoride (PMSF), respectively. Tissue homogenates were preincubated with each inhibitor (final concentration, 5 mM) at 4 °C for 30 min before measurement of residual proteolytic activity under identical assay conditions. The activity of each protease class was calculated as the difference between total proteolytic activity measured in the absence of inhibitor and residual activity measured in the presence of the corresponding inhibitor.

Substrate gel electrophoresis (gelatin zymography). Gelatin zymography was performed according to the method of Ostapchenko et al. [16] with minor modifications. Samples containing 20 µg of total protein were mixed (1:1, v/v) with sample buffer (5 mM Tris-HCl, pH 8.8, 2 % SDS, 5 % sucrose, and 0.02 % bromophenol blue) and separated by electrophoresis under non-reducing conditions in 12 % polyacrylamide gels copolymerized with gelatin (1 mg/ml). Electrophoresis was performed at a constant current of 19 mA. Following electrophoresis, gels were washed twice in 2.5 % Triton X-100 for 30 min to remove SDS and restore enzymatic activity and then incubated in 50 mM Tris-HCl buffer (pH 7.4) containing 0.13 M NaCl at 37 °C for 12 h. Gels were subsequently stained with 2.5 % Coomassie Brilliant Blue R-250 and destained until clear gelatinolytic bands became visible against a dark blue background. Apparent molecular weights (MW) were estimated using protein MW standards. Gelatinolytic bands were quantified densitometrically using TotalLab CLIQS version 2.04 (TotalLab Ltd., Newcastle upon Tyne, UK). Band intensity was expressed as the percentage of the total integrated band density within each electrophoretic lane.

The protein concentration in skin homogenates was determined according to the Bradford method using bovine serum albumin (BSA) as the standard. Absorbance was measured at 595 nm.

Statistical analysis. Statistical analysis was performed using Statistica version 13.3 (TIBCO Software Inc., Palo Alto, CA, USA). Data are presented as mean ± standard deviation (SD). Differences among experimental groups were evaluated using one-way analysis of variance (ANOVA). A value of $p < 0.05$ was considered statistically significant.

Results and discussion. To evaluate obesity-associated alterations in proteolytic homeostasis following wound healing, total proteolytic activity and the activities of metal-dependent and serine proteases were determined in skin homogenates. Total proteolytic activity increased progressively across the experimental groups (Fig. 1). Compared with intact controls, total proteolytic activity increased approximately 2.01-fold in the MGI-Ob group and 3.41-fold in the Wound group, whereas the highest activity (4.29-fold vs. control) was detected in obese wounded animals ($p < 0.05$). Furthermore, total proteolytic activity remained significantly higher in obese wounded rats than in both obese (2.13-fold) and non-obese wounded (1.35-fold) animals ($p < 0.05$ for both comparisons), indicating that obesity is associated with enhanced proteolytic activity that persists after complete macroscopic wound closure (Fig. 1).

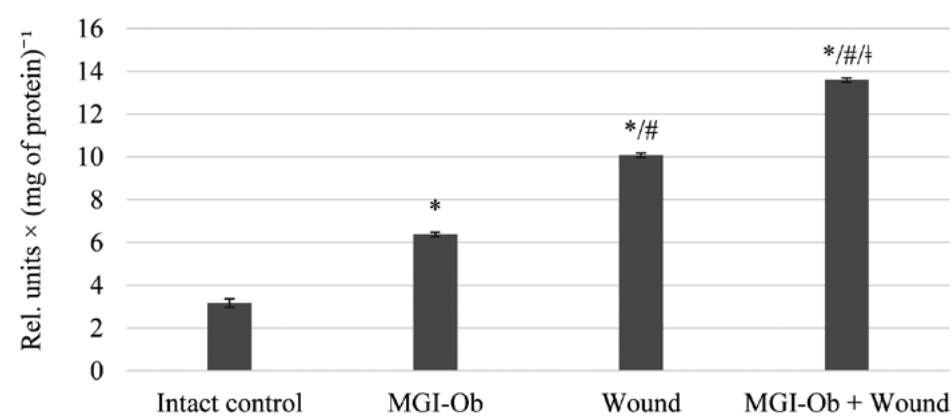


Fig. 1. Total proteolytic activity in skin homogenates of rats with monosodium glutamate-induced obesity (MGI-Ob) following experimental cutaneous wounding. Data are presented as mean $\pm$ SD (n = 10); *p < 0.05 vs. the Intact control group; #p < 0.05 vs. the MGI-Ob group; ‡p < 0.05 vs. the Wound group

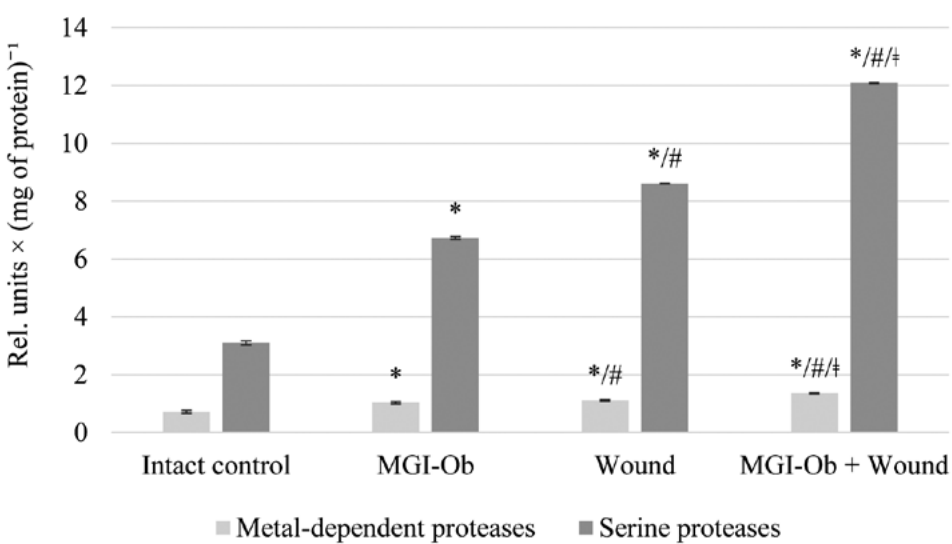


Fig. 2. Enzymatic activities of metal-dependent and serine proteases in skin homogenates of rats with monosodium glutamate-induced obesity (MGI-Ob) following experimental cutaneous wounding. Data are presented as mean $\pm$ SD (n = 10); *p < 0.05 vs. the Intact control group; #p < 0.05 vs. the MGI-Ob group; ‡p < 0.05 vs. the Wound group

To determine which proteolytic systems contributed to the observed increase in total proteolytic activity, the activities of metal-dependent and serine proteases were assessed using selective inhibition with EDTA and PMSF, respectively. Metal-dependent protease activity increased only modestly, reaching 1.45-, 1.56-, and 1.92-fold of intact control values (p < 0.05) in the MGI-Ob, Wound, and MGI-Ob + Wound groups, respectively (Fig. 2). In contrast, serine proteases exhibited a markedly greater increase, reaching approximately 2.17-, 2.78-, and 3.90-fold of intact control values (p < 0.05) in the MGI-Ob, Wound, and MGI-Ob + Wound groups, respectively (Fig. 2). These results indicate that serine proteases contributed more substantially than metal-dependent proteases to the increase in total proteolytic activity. This pattern is consistent with the coordinated involvement of multiple protease systems in ECM remodeling during wound healing [17]. The persistently elevated proteolytic activity after complete macroscopic wound closure indicates persistent dysregulation of

proteolytic homeostasis in healed skin. In our previous study [18] using the same experimental model, we demonstrated delayed wound healing together with obesity-associated metabolic disturbances, providing phenotypic evidence of impaired tissue repair. Our findings are also in agreement with previous studies reporting delayed wound healing accompanied by altered expression of growth factors, MMPs, and tissue inhibitors of MMPs (TIMPs) in rats with MGI obesity [19]. The present findings extend these observations by demonstrating that obesity-associated impairment of wound healing is accompanied by sustained activation of proteolytic systems even after complete wound closure. The markedly greater activation of serine protease compared with metal-dependent proteases suggests that serine proteases may represent the predominant drivers of ECM turnover during the late remodeling phase. Given that serine proteases participate both in direct ECM degradation and in the activation of latent MMPs, their sustained activation may promote prolonged matrix turnover and delayed restoration of proteolytic homeostasis during the remodeling phase [17].

To further characterize the gelatinolytic proteases underlying the observed increase in proteolytic activity, gelatin zymography was performed. Gelatin zymography revealed marked qualitative differences in gelatinolytic profiles among the experimental groups (Table 1). In the intact control group, the predominant gelatinolytic band corresponded to putative active MMP-13, accounting for 77.18 % of the total gelatinolytic activity, followed by pro-MMP-2, which accounted for 22.47 %. In the MGI-Ob group, an additional band corresponding to putative active MMP-2 appeared together with a reduced relative contribution of putative active MMP-13, indicating increased heterogeneity of the gelatinolytic profile. Following wound healing in non-obese animals, putative active MMP-2 became the predominant gelatinolytic band and was accompanied by the appearance of low-MW gelatinolytic fragments. The most pronounced alterations were observed in the MGI-Ob + Wound group, in which low-MW gelatinolytic fragments accounted for approximately 93 % of total gelatinolytic activity, whereas putative active MMP-2 and MMP-13 represented only minor components (5.81 % and 1.23 %, respectively). The pro-MMP-2 band was no longer detected (Table).

Table

Apparent molecular weights, putative identities, and relative intensities of gelatinolytic bands detected by gelatin zymography in skin homogenates from rats in the experimental groups

Group	MW, kDa	Putative identity	Band intensity (% of total)
Intact control	71	pro-MMP-2	22.47
	49	active MMP-13	77.18
	22	low-molecular-weight gelatinolytic fragment	0.35
MGI-Ob	74	pro-MMP-2	31.17
	63	active MMP-2	22.90
	49	active MMP-13	45.73
	23	low-molecular-weight elatinolytic fragment	0.20
Wound	72	pro-MMP-2	23.76
	61	active MMP-2	36.92
	47	active MMP-13	9.14
	28	low-molecular-weight gelatinolytic fragment	3.09
	23	low-molecular-weight gelatinolytic fragment	27.09
MGI-Ob + Wound	63	active MMP-2	5.81
	47	active MMP-13	1.23
	22	low-molecular-weight gelatinolytic fragment	92.96

Note. Relative band intensity is expressed as the percentage of total lane density. Band identities are putative and based on apparent molecular weights.

Collectively, these findings demonstrate that obesity was associated not only with increased proteolytic activity but also with profound qualitative remodeling of the gelatinolytic protease profile. Specifically, obesity was accompanied by a progressive shift in the distribution of gelatinolytic proteases toward the predominance of low-MW gelatinolytic fragments. Similar alterations in MMP profiles have been reported in adipose tissue and other rat tissues, supporting the concept that obesity promotes tissue-specific remodeling of proteolytic systems [20, 21].

Because gelatinolytic bands were identified solely according to their electrophoretic mobility, their molecular identities remain putative. Likewise, the low-MW gelatinolytic fragments cannot be unequivocally assigned to specific enzymes without additional biochemical or immunological characterization. Nevertheless, the marked predominance of low-MW gelatinolytic fragments in obese wounded animals suggests sustained proteolytic processing during the late remodeling phase of wound healing. These observations are consistent with current concepts of chronic wound pathology, in which persistent activation and processing of MMPs contribute to excessive ECM degradation and delayed restoration of tissue homeostasis [22]. Overall, gelatin zymography demonstrated progressive qualitative remodeling of the gelatinolytic protease profile during wound healing under obese conditions, characterized by a marked shift from high-molecular-weight gelatinolytic forms to the predominance of low-MW gelatinolytic fragments.

Conclusion. The present study demonstrates that MGI obesity is associated with pronounced alterations in the proteolytic system of healed skin following experimental cutaneous wounding. Experimental obesity resulted in persistent elevation of total proteolytic activity, with serine proteases contributing more substantially than metal-dependent proteases to the overall proteolytic response. Gelatin zymography revealed progressive remodeling of the gelatinolytic protease profile, characterized by redistribution of gelatinolytic activity from the predominance of putative active MMP-13 in the intact control group to the predominance of low-MW gelatinolytic fragments following wound healing under obese conditions.

Collectively, these findings indicate persistent impairment of proteolytic homeostasis after wound closure under obese conditions, reflected by sustained proteolytic activation and qualitative remodeling of the gelatinolytic protease profile. Future studies are warranted to identify the molecular nature of the low-MW gelatinolytic fragments and to clarify their role in ECM remodeling and tissue repair during obesity-associated wound healing.

Conflicts of interest. The authors declare no competing interests.

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