ФИБРОГЕННЫЙ И ФИБРОЛИТИЧЕСКИЙ ПОТЕНЦИАЛ РАЗЛИЧНО АКТИВИРОВАННЫХ МАКРОФАГОВ ЧЕЛОВЕКА

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Резюме. Макрофаги участвуют в регуляции фиброгенеза и процессе синтеза/деградации внеклеточного матрикса. Одним из способов реализации данной функции является продукция ими фиброгенных и фибролитических факторов, включая фибронектин, ламинин, коллаген, а также протеазы внеклеточного матрикса. Продукция большинства из них хорошо изучена в экспериментальных моделях на животных, однако в отношении макрофагов человека все еще остается много неясностей. Поэтому целью настоящего исследования являлось изучение содержания протеаз внеклеточного матрикса (MMP-2 и MMP-9, катепсина L), их ингибиторов (TIMP-1) и коллагена (I типа) в супернатантах различно активированных макрофагов человека. Нами было проведено сравнение макрофагов, дифференцированных M-CSF или GM-CSF и далее поляризованных в M1 липополисахаридом, в M2a – IL-4 и в M2c – дексаметазоном. Макрофаги получали из моноцитов периферической крови условно здоровых доноров. Содержание MMP, TIMP, катепсина и коллагена определяли с помощью соответствующих наборов иммуноферментного анализа. Согласно полученным результатам, дифференцировочные факторы играют более важное значение для продукции вышеперечисленных веществ по сравнению с поляризующими стимулами (липополисахарид, IL-4, дексаметазон). При этом макрофаги, дифференцированные M-CSF, проявляли преимущественно антифиброгенную активность благодаря выраженной продукции MMP, тогда как GM-CSF-индуцированные культуры, напротив, характеризовались профиброгенными свойствами за счет высокого уровня TIMP-1 и коллагена I типа. M1, M2a и M2c, индуцированные M-CSF, различались только по уровню продукции MMP-2, причем M2a активнее продуцировали данную металлопротеиназу по сравнению с другими подтипами. Среди GM-CSF-дифференцированных макрофагов более высокий уровень продукции TIMP-1 и, в меньшей степени, коллагена I типа был характерен для M1, тогда как супернатанты M2c отличались минимальной концентрацией указанных факторов. Что касается уровня продукции катепсина L, то он был относительно постоянным и не зависел от условий генерации макрофагов (дифференцировочных и поляризующих сигналов). Таким образом, полученные нами данные помогают идентифицировать подтипы макрофагов с анти- или профиброгенным потенциалом и могут быть полезны для разработки клеточной терапии заболеваний, связанных с нарушением регуляции фиброгенеза.

Ключевые слова: макрофаги, матричные металлопротеиназы, коллаген, катепсин, фиброз, антифиброгенная активность

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FIBROGENIC AND FIBROLYTIC POTENTIAL OF DIFFERENTLY ACTIVATED HUMAN MACROPHAGES

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Abstract. Macrophages are involved in the regulation of fibrogenesis and turnover of the extracellular matrix. One way to perform this function is through the production of profibrotic and fibrolytic factors including fibronectin, laminin, collagen, and extracellular matrix proteases. The production of most of them has been well studied in experimental models; however, much remains unclear regarding human macrophages. Therefore, the aim of this study was to study the content of extracellular matrix proteases (MMP-2 and MMP-9, cathepsin L), their inhibitors (TIMP-1), and collagen (type I) in supernatants of differently activated human macrophages. We compared macrophages differentiated by M-CSF or GM-CSF and further polarized in M1 with lipopolysaccharide, in M2a with IL-4, and in M2c with dexamethasone. Macrophages was obtained from peripheral blood monocytes. The content of MMPs, TIMP, cathepsin, and collagen was determined using appropriate ELISA kits. The results obtained demonstrate that differentiation factors are more important for the production of the above factors compared to polarizing stimuli (lipopolysaccharide, IL-4, dexamethasone). Moreover, macrophages differentiated by M-CSF showed predominantly antifibrotic activity because of pronounced MMPs production, while GM-CSF-induced cultures, on the contrary, were characterized by profibrotic properties due to the high level of TIMP-1 and type I collagen. M1, M2a, and M2c, induced by M-CSF, differed only in MMP-2 production, and M2a produced this metalloproteinase more than other subtypes. In the case of GM-CSF-differentiated cells, a higher level of production of TIMP-1 and, to a lesser extent, type I collagen was characteristic of M1, whereas M2c have minimal concentration of them among GM-CSF-induced macrophage subtypes. Concerning the level of cathepsin L production was relatively constant and did not depend on the generation conditions (differentiation and polarizing signals). Thus, the data obtained help to identify macrophage subtypes with anti- or profibrotic potential and may be useful for the development of cell therapy for diseases associated with fibrogenesis dysregulation.

Keywords: macrophages, matrix metalloproteinase, collagen, cathepsin, fibrosis, anti-fibrotic activity

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Introduction

Macrophages are the central players in the innate immunity. Due to amazing plasticity, these cells are involved in the regulation of many processes in the human body, including regeneration and tissue remodeling. The ability to produce various biologically active substances allows macrophages to directly influence the turnover of the extracellular matrix (ECM) through the synthesis and secretion of metalloproteinases (MMPs) and other enzymes for ECM degradation. Moreover, it has recently been shown that macrophages directly contribute to the heart regeneration and fibrosis by collagen production [13].

However, there are still many unexplored questions regarding human macrophages. First, animal and human macrophages differ significantly, e.g., in the spectrum and expression level of mRNA of MMPs and TIMPs [10], so the data obtained on experimental models require confirmation in the human. Second, most human macrophage research has been done on classically and alternatively activated macrophages (generally termed M1 and M2a), whereas other subtypes are still incompletely described (M2b, M2c, M2d, etc.) [3, 11]. Finally, many researchers use different differentiation factors to obtain M1 and M2 cells (GM-CSF and M-CSF, respectively), while the conditions of differentiation largely influence the macrophage functional phenotype [5].

Thus, **the aim of our study** was to study how differentiation and polarization signals affect the production of fibromodulatory factors by macrophages, including matrix metalloproteinases (MMP-2 and MMP-9), tissue inhibitors of metalloproteinases (TIMP-1) and collagen, and to determine macrophage phenotypes with a more profibrotic or fibrolytic potential.

Materials and methods

The study included 63 healthy donors of both sexes aged 22-60 years. Mononuclear cells were isolated by centrifugation of heparinized venous blood in a ficoll-verografin density gradient and then cultured in an amount of $4\text{-}5 \times 10^6$/mL in 12-well plates (TPP, Switzerland) in RPMI-1640 medium (BioloT, Russia) supplemented with 10% fetal bovine serum (Biowest, USA) and 50 ng/mL recombinant M-CSF or GM-CSF (Sigma-Aldrich, USA). After 1 hour, the non-adherent fraction of cells was removed, and the adhesive one continued to be cultured for 7 days. On the 5th day, appropriate polarizing stimuli were added to the cultures: 10 μg/mL LPS (*E. coli* 0114:B4, Sigma-Aldrich, USA) to obtain M1; 20 ng/mL IL-4 (Sigma-

Aldrich, USA) – to M2a; 50 ng/mL dexamethasone (Dex) (KRKA, Slovenia) – to M2c. The supernatants were collected, centrifuged, cryopreserved and stored at -80 °C.

The level of production of MMP-9, MMP-2, TIMP-1, cathepsin L, and type I collagen in supernatants of 7-day-old macrophage cultures was assessed using enzyme immunoassay. To determine the concentration of MMP-2, MMP-9, and TIMP-1, the corresponding ELISA kit (all R&D System kits, USA) was used in accordance with the manufacturer's instructions. Human Cathepsin L Platinum ELISA (Invitrogen, USA) was used to determine the level of cathepsin L production in accordance with the manufacturer's instructions. The level of collagen production was determined by the concentration of the α1-chain of type I collagen using the Human COL1A1 (Collagen Type I Alpha 1) ELISA Kit (FineTest, China) in accordance with the manufacturer's instructions. The data were recalculated per 100,000 cells.

The significance of statistical differences between the compared groups was assessed using nonparametric Wilcoxon matched pair test and Mann–Whitney U test; the differences were considered significant at $p < 0.05$.

Results and discussion

Initially, we analyzed the content of ECM proteases in the supernatants of M- and GM-CSF-differentiated macrophages. MMP-2 and MMP-9 were chosen for assessment because they are important for fibrogenesis and are the most well produced by human macrophages. Figure 1A shows that the level of MMP-2 in the supernatants of M-CSF-differentiated cells was significantly higher compared to GM-CSF-differentiated analogs. For example, M1(LPS) in the presence of M-CSF produced MMP-2 at a level of 3050 pg/mL, while that in the presence of GM-CSF reached only 33 pg/mL. The content of MMP-2 in M-CSF-differentiated M2a(IL-4) supernatants was more than 100 times higher than that of GM-CSF-induced analogs (5450 and 48 pg/mL, respectively, $p_U < 0.01$), and in M2c(Dex) was more than 70 times higher (2730 and 40 pg/mL, respectively, $p_U < 0.01$). At the same time, among M-CSF-differentiated macrophages, M2a(IL-4) were characterized by a higher MMP-2 value compared to M1(LPS) and M2c(Dex) ($p_W < 0.05$ and $p_W = 0.06$, respectively). No significant differences were found among GM-CSF-differentiated M1(LPS), M2a(IL-4), and M2c(Dex).

Next, we determined the content of MMP-9 (Figure 1B). In general, human macrophages produced this metalloproteinase more actively than MMP-2 (6500-11,000 *vs* 30-5500 pg/mL, respectively). At the same time, the level of MMP-9 in cultures of M-CSF-differentiated macrophages was on average 1.5-1.7 times higher compared to cells differentiated by GM-CSF. M-CSF- and GM-CSF-induced M1(LPS) (10170 *vs* 6770 pg/mL) and M2c(Dex) (11000 *vs* 6540 pg/mL) differed significantly from each other ($p_U < 0.05$). As for M2a(IL-4), despite the fact that in general, M-CSF-induced cells produced more MMP-9 compared to GM-CSF (9330 *vs* 6770 pg/mL), no significant differences were found between subtypes. At the same time, polarizing stimuli apparently had a less significant effect on the level of MMP-9 production, since statistical differences were not found among M1(LPS), M2a(IL-4) and M2c(Dex), differentiated by the same factor.

TIMPs are specific inhibitors of metalloproteinases. M-CSF induced the cells with equally low TIMP-1-producing activity for all subtypes (Figure 1C) (at the lower sensitivity level of the method, ≤ 80 pg/mL). However, GM-CSF-differentiated macrophages quite actively produced this inhibitor (1450-3800 pg/mL). TIMP-1 production by M1(LPS) was the highest (3080 pg/mL) and significantly exceeded M2c(Dex) and M2a(IL-4) at the trend level (1450 and 2100 pg/mL, respectively, $p_W = 0.004$ and 0.06). On the contrary, M2c(Dex) were characterized by a minimal level of TIMP-1 compared to other subtypes of GM-CSF-differentiated cells ($p_W < 0.05$).

Cathepsin L is the one of the proteases for which ECM is a substrate. Figure 1D demonstrates that macrophages produced cathepsin L at relatively the same level, regardless of the differentiation and polarizing stimuli. Thus, M-CSF-differentiated M1(LPS) did not differ significantly from M2a(IL-4) and M2c(Dex), although Cathepsin L concentration in the M2c(Dex) supernatants was slightly higher compared to the other macrophage subtypes (2350 pg/mL *vs* 1650 and 1510 pg/mL, respectively). GM-CSF-differentiated M1(LPS), M2a(IL-4), M2c(Dex) also did not differ in cathepsin L production (1600, 1480, and 1330 pg/mL, respectively).

Finally, the production of type I collagen by human macrophages was investigated. It turned out that all the studied macrophage subtypes produced collagen I at a well-detectable level (Figure 1E). In general, except M2c(Dex), M-CSF-differentiated macrophages had a significantly lower level of collagen I production compared to GM-CSF analogs. Actually, the concentration of collagen in M-CSF-differentiated M1(LPS) supernatants was more than 2.5 times lower than that in GM-CSF-induced M1(LPS) cultures (3350 *vs* 8100 pg/mL, respectively; $p_U = 0.05$). M2a(IL-4) differentiated M-CSF also had lower levels of collagen I compared to GM-CSF analogs (4740 *vs* 7000 pg/mL, $p_U < 0.05$). However, no significant differences were found between M1(LPS), M2a(IL-4), and M2c(Dex) differentiated by M-CSF factor.

MMPs and TIMPs are the most important mediators of ECM turnover, so the ability of macrophages to produce these factors at high concentrations is believed to reflect their ability to maintain tissue homeostasis through ECM remodeling [15]. MMPs degrade ECM proteins, predominantly collagen, while TIMPs are specific inhibitors of MMPs.

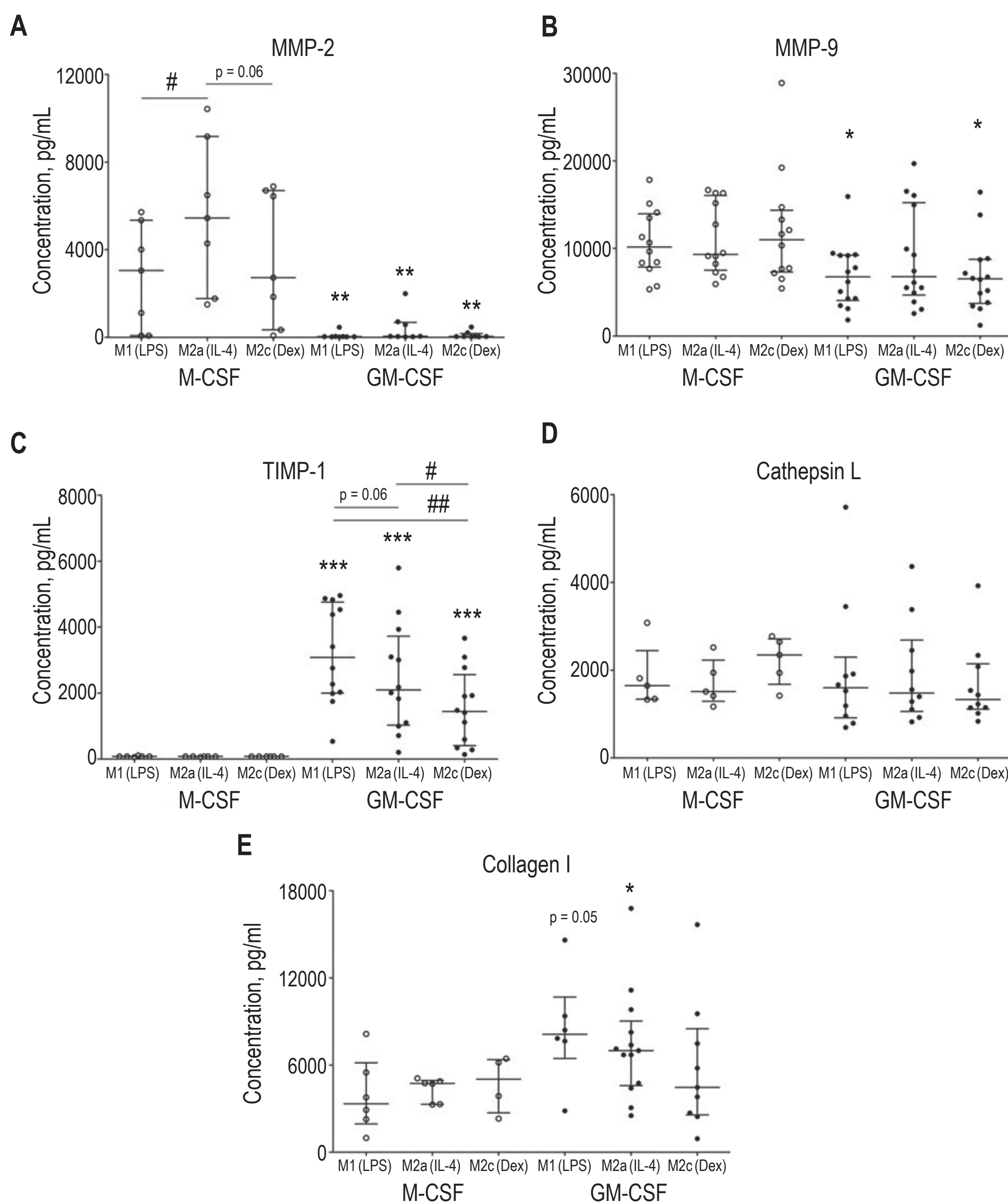

Figure 1. Production of profibrotic and fibrolytic factors by differently activated human macrophages

Note. (A) Production of MMP-2 by macrophage subtypes, n = 7-8. (B) Production of MMP-9 by macrophage subtypes, n = 12-14. (C) Production of TIMP-1 by macrophage subtypes, n = 6-12. (D) Production of cathepsin L by macrophage subtypes, n = 5-10. (E) Production of collagen I by macrophage subtypes, n = 4-13. Data are presented as individual values, median and interquartile range; *, $p_U < 0.05$; **, $p_U < 0.01$; ***, $p_U < 0.001$ statistical difference with M-CSF-induced cells. The line indicates the differences between the indicated macrophage subtypes; #, $p_W < 0.05$; ##, $p_W < 0.01$.

The expression of MMPs and TIMPs in cells and tissues is specific and depends on many factors. The synthesis of MMPs and TIMPs is controlled by various microenvironmental signals such as cytokines and growth factors. Moreover, the expression of various MMPs can be stimulated or suppressed by integrin signals, ECM proteins, and cell shape changes. In general, the level of MMP production outside of pathology is quite low, but it significantly increases in tissues during wound healing, repair, and remodeling [10].

Human macrophages produce the wide spectrum of MMPs, as well as TIMPs, and their production depends on the stage of maturation/cell differentiation and the polarization state of macrophages. In general, the expression of most MMPs (MMP-2, MMP-7, MMP-9, etc.) is significantly increased during the differentiation of monocytes into macrophages [10]. At the same time, differentiation factors, such as M-CSF or GM-CSF, can affect the spectrum of MMPs and TIMPs produced. Here we demonstrate that in relation to MMP-2 and MMP-9 production, M-CSF increases MMP levels more than GM-CSF, and this is consistent with the study of Aristorena et al., which indicated that mRNA MMP-2 and

MMP-9 were more strongly expressed in M-CSF-stimulated macrophages (although the differences were not too pronounced) [1].

In addition, various activation signals (LPS, IFNγ, TNFα, IL-1β, IL-4, IL-10) influence the MMP and TIMP profile [6, 7]. However, the data obtained are often contradictory. So, Huang et al. showed that the polarization of macrophages towards M1 phenotype increases the mRNA expression of MMP-1 and MMP-12 along with decrease in MMP-2 expression. As for MMP-9 and TIMP-1, there is no difference between M1 and M2 cells [6]. On the contrary, Jager et al. revealed an increase in MMP-1, MMP-9, MMP-12 and TIMP-1 expression after M2 polarization, while M1 and M2 cells did not differ in the MMP-2 expression [7]. Most likely, these differences are due to the different protocols for the generation of macrophages. Of note, the authors utilized M-CSF for macrophage generation. Along with Huang's study, we also found higher levels of MMP-2 in M-CSF-induced M2a(IL-4) cultures compared to M1(LPS), and showed that there is no significant difference on MMP-9 production between M1(LPS), M2a(IL-4), and M2c(Dex).

TIMP-1 production reflects the profibrotic capacity of cells, and high values of this inhibitor were found in progressive fibrosis in humans and in experimental animals. On the contrary, during the resolution of fibrosis, there is a rapid decrease in the TIMP level and a change in the overall balance of MMP/TIMP, accompanied by an increase in the rate of ECM degradation [2]. In addition, TIMPs can influence fibrogenesis by regulating the growth of various cell types, in particular, by stimulating proliferation of fibroblasts [9]. According to our results, GM-CSF directs macrophage differentiation to a more profibrotic phenotype compared to M-CSF. In contrast to Jager et al., who showed a higher level of TIMP-1 in M-CSF- differentiated macrophages with the M2 phenotype at the level of mRNA expression [7], we did not reveal any differences between M1 and M2 at the protein level. But this discrepancy may be insubstantial, since the level of production often is not in line with the level of gene expression.

Here, we also studied for the first time the production of such an important ECM protease as cathepsin L by differently activated human macrophages. Our data show that macrophages produce cathepsin L at a well-detectable level (1300-2300 pg/mL), which is relatively constant regardless of microenvironmental conditions.

Collagen is the predominant component of ECM playing an important structural role and largely determines the mechanical properties, organization, and structure of tissues. An increase in the collagen amount is associated with the development of fibrosis. It is believed that fibrillar collagens, and especially type I collagen, are of paramount importance. Thus, type I collagen has been shown to be involved in the pathogenesis of pulmonary and hepatic fibrosis, systemic scleroderma, and hypertrophic scars [8].

It was previously thought that all collagens are secreted exclusively by fibroblasts, but it is now known that certain types of collagens can be produced by numerous epithelial cells as well as by macrophages. Several studies in animal models have demonstrated that macrophages express collagen mRNA and isoforms of collagen-associated genes, and are capable of producing various types of collagens, in particular, type I collagen [13, 14]. Moreover, by producing collagen, macrophages directly contribute to the development of cardiac fibrosis [13]. Recent studies suggest that collagen production by macrophages is an important link in the pathogenesis of fibrosis and regeneration [14].

In humans, the ability of macrophages to produce collagen has also been demonstrated. Indeed, Schnoor et al. showed that monocyte-derived macrophages expressed mRNA of all collagen types (except XIII and XXII) are capable of producing type VI collagen [12]. In another study, the high level of expression of mRNA of various types of collagens (IV, VI, VIII, etc.) was also confirmed [4].

Here we first demonstrate that human macrophages are capable of producing type I collagen. Moreover, the level of production of this protein is largely determined by the conditions of macrophage differentiation (M-CSF or GM-CSF), while polarizing stimuli have a less significant effect. Differentiation stimuli can act directly on collagen mRNA expression and its further production or indirectly through the regulation of the MMP/TIMP balance, which in turn affects collagen degradation.

Conclusion

In summary, M-CSF-differentiated macrophages in general exhibit more fibrolytic properties due to the higher level of production of MMP-2 and MMP-9, along with a low value of TIMP-1 and collagen I, while GM-CSF, on the contrary, promotes profibrotic activity of macrophages. At the same time, polarization in the M1, M2a, M2c direction in the presence of M-CSF slightly affects the production of the studied factors (differences were found only for MMP-2 production). In the case of GM-CSF-differentiated cells, the differences were also not very noticeable. However, in general, it can be concluded that a higher level of production of TIMP-1 and, to a lesser extent, collagen I was characteristic of M1(LPS). In contrast, M2c(Dex) have minimal concentration of them among GM-CSF-induced macrophage subtypes. Thus, the results obtained help to identify macrophage subtypes with anti- or profibrotic potential and may be useful for the development of cell therapy for diseases associated with fibrogenesis dysregulation.

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