DETERMINATION OF AGING PHENOTYPE BASED ON THE CHANGES IN SPONTANEOUS AND INDUCED INTERLEUKIN-6 AND INTERLEUKIN-10 PRODUCTION *IN VITRO*

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During the aging the immune system alterations are accompanied by developing the systemic, sterile inflammation: inflammaging. Successful and pathological aging phenotypes are distinguished. Inflammaging severity depends largely on the ratio of pro- and anti-inflammatory mediators, especially IL6 and IL10. The study aimed to conduct the analysis of IL6 and IL10 production in the cultures of the patients' peripheral blood mononuclear cells (MNCs) as a possible approach to determining the aging phenotype. The data of elderly patients (n = 80), senile patients (n = 100), and centenarians (n = 30) were included in the study. Among those the groups were allocated with the successful and pathological phenotypes, along with the comparison group (young adults). The stimulation coefficient (SC) was assessed based on the ratio of the levels of stimulated and induced cytokine production. For the successful phenotype in elderly and senile individuals, as well as centenarians, a decrease in the IL6 SC to 5.3 [2.2–14.3] (p < 0.01), 5.3 [3.01–7.8] (p < 0.01), 6.5 [5.2–14.1], respectively, was reported, against the comparison group, where the value was 17.6 [13.7–31.1] (p < 0.05). With the pathological phenotype, the IL6 SC values of the studied age group showed no significant differences from that of the comparison group. For the successful phenotype in senile individuals, the increase in the IL10 SC to 6.9 [3.8–13.8] relative to the values of the group with the pathological phenotype — 3.3 [2.0–5.9] (p < 0.01) and the comparison group — 2.0 [1.9–2.2] (p < 0.001) was reported. In the group of centenarians with the pathological phenotype, there was a significant increase in the IL10 SC (11.2 [5.4–18.1] vs 2.7 [2.3–6.5] p < 0.001) in the group with successful aging, which can indicate the pronounced compensatory anti-inflammatory reserve being a factor of survival and long life in the context of the presence of a large number of age-related disorders in this group.

Keywords: inflammaging, cytokines, cell culture, aging phenotype, markers of aging

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ОПРЕДЕЛЕНИЕ ФЕНОТИПА СТАРЕНИЯ ПО ИЗМЕНЕНИЮ СПОНТАННОЙ И ИНДУЦИРОВАННОЙ ПРОДУКЦИИ ИНТЕРЛЕЙКИНА-6 И ИНТЕРЛЕЙКИНА-10 *IN VITRO*

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В процессе старения изменения в иммунной системе сопровождаются развитием системного стерильного воспаления «inflammaging». Выделяют успешный и патологический фенотипы старения. Степень развития «inflammaging» во многом зависит от соотношения про- и противовоспалительных медиаторов, особенно ИЛ-6 и ИЛ-10. Целью исследования было провести анализ продукции ИЛ-6 и ИЛ-10 в культурах мононуклеарных клеток (МНК) периферической крови пациентов как возможного подхода определения фенотипа старения. В работу включены данные пациентов пожилого возраста (n = 80), старческого возраста (n = 100) и долгожителей (n = 30), среди которых выделены подгруппы с успешным и патологическим фенотипами, а также группы сравнения (молодых лиц). Проводили оценку коэффициента стимуляции (КС) по соотношению уровней стимулированной и спонтанной выработки цитокинов. Для успешного фенотипа в пожилом, старческом возрасте и у долгожителей выявлено снижение КС ИЛ-6 до 5,3 [2,2–14,3] (p < 0,01), 5,3 [3,01–7,8] (p < 0,01), 6,5 [5,2–14,1] соответственно, по отношению к группе сравнения, где показатель составил 17,6 [13,7–31,1] (p < 0,05). При патологическом фенотипе показатели КС ИЛ-6 исследуемых возрастных групп достоверно не отличались от группы сравнения. Для успешного фенотипа в старческом возрасте выявлено повышение КС ИЛ-10 до 6,9 [3,8–13,8] по отношению к уровню группы патологического фенотипа — 3,3 [2,0–5,9] (p < 0,01) и группы сравнения — 2,0 [1,9–2,2] (p < 0,001). В группе долгожителей при патологическом фенотипе значительно повышался КС ИЛ-10 (11,2 [5,4–18,1] против 2,7 [2,3–6,5] p < 0,001) в группе успешного старения, что может свидетельствовать о выраженном компенсаторном противовоспалительном резерве, являющемся фактором выживания и долголетия при наличии большого количества возраст-ассоциированных заболеваний в данной группе.

Ключевые слова: воспалительное старение, цитокины, культура клеток, фенотип старения, маркеры старения

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An increase in life expectancy and a dramatic increase in the share of elderly people in the structure of the population attract a lot of interest to the studies of aging mechanisms. Aging affects all systems of the body, including the immune system that contributes greatly to shaping the aging trajectories. The inflammaging theory is currently one of the key theories of aging [1]. According to this theory, the chronic sterile low-grade inflammation is developed during aging, which can contribute to the age-associated disorders. Various factors, such as oxidative stress, impaired autophagy, emergence of senescent cells, microbiota composition alteration, inflammasome activation, etc., can cause such inflammation [2]. All the above factors lead to the increase in DAMP (damage-associated molecular patterns) and PAMP (pathogen-associated molecular patterns), and, therefore, to the increased production of pro-inflammatory cytokines, chemokines. Two aging phenotypes are distinguished based on the inflammation severity: successful and pathological aging. Successful aging is associated with reaching the optimal levels of physical, cognitive, and psycho-social adaptation in the elderly. Pathological aging, in contrast, is associated with faster aging, development of age-associated disorders resulting in disability and decline in quality of life [3]. In this regard, the search for approaches determining the aging phenotype is a relevant task.

There are extensive data on the cytokine system alteration during aging in the literature [4, 5]. However, there are currently almost no papers considering alterations of pro- and anti-inflammatory cytokines in broad age range in terms of successful and pathological aging phenotypes. It has been shown that the pathological aging phenotype in senile individuals is characterized by the increase in serum concentrations of pro-inflammatory cytokines (IL6, TNF, IL18), while the levels of anti-inflammatory cytokines, such as IL10 and TGF, in contrast, decrease compared to that of young adults [6]. However, systemic cytokine levels do not answer the question, how the immune system cells will respond to infectious stimuli or damage, which can be important in the context of assessing the prognosis of the infectious disease, such as COVID-19, or the course of the age-associated disorder. Furthermore, the levels of the most indicative cytokines, such as IL6 and IL10, in peripheral blood of patients showing no clinical manifestations of systemic inflammation, are still low, literally on the lower sensitivity limit of modern diagnostic test systems, which makes assessment of these indicators in clinics as the diagnostic and prognostic inflammaging markers rather controversial. In this regard, the analysis of the spontaneous and induced cytokine production by mononuclear cells (MNCs) in in vitro cultures seems to be more informative in terms of determining the aging phenotype.

The study aimed to perform the analysis of spontaneous and bacterial lipopolysaccharide (LPS)-induced IL6 and IL10 production in the cultures of peripheral blood MNCs from patients of older age groups with different aging phenotypes.

METHODS

The following subjects were included in the study:

– 80 elderly individuals (average age 68.7 ± 4.3 years, among them 53 females, 27 males);

– 100 senile patients (average age 81.8 ± 5.3 years, among them 72 females, 28 males);

– 30 centenarians (average age 92.7 ± 1.7 years, among them 21 females, 9 males).

All the patients were examined at the Geriatric Center, Moscow Diagnostic Clinical Center No. 1.

Exclusion criteria: acute disorder or exacerbation of chronic disorder at the time of enrollment. Inclusion criteria: subject's age corresponding to the studied group; availability of the submitted informed consent to participation in the study.

To assess the aging phenotype, the comprehensive geriatric assessment (CGA) was conducted that included evaluation of somatic status (Charlson Comorbidity Index, CCI), physical health (Short Physical Performance Battery, SSPB), and cognitive functions (Mini-Mental State Examination, MMSE). The criteria for dividing into subgroups with successful and pathological aging are provided in the Table.

The comparison group included 25 young adults (average age 22.4 ± 2.8 years), among them 16 females and 9 males. All the young adults enrolled had no acute or chronic disorder at the time of enrollment, as well as no limitation of physical functioning or cognitive impairment. Inclusion criteria: subjects in young adulthood; availability of the submitted informed consent to participation in the study. Exclusion criteria: acute or chronic disorder.

Peripheral blood samples were used as biomaterial for the study.

MNCs for culturing were isolated from peripheral blood on the Ficoll–Urografin density gradient medium (p = 1.077 g/cm3) [8]. The cells isolated were cultured for 24 h in the RPMI-1640 medium (Capricorn cop., USA) supplemented with the 20% fetal calf serum (Panexin, GMbH, Germany) at the temperature of 37 °C and 5% CO_2. The concentration of cells during culturing was 1×10^6 cells/mL. To assess the stimulated cytokine production, a bacterial LPS (Servicebio, China) with the nominal concentration of 0.1 μg/mL was added to the cells. Spontaneous cytokine production was assessed in the cell culture not supplemented with the LPS or other stimulator.

The IL6 and IL10 cytokine concentration was determined in the cell culture supernatant by enzyme-linked immunoassay using the commercially available test systems (Vector-Best, Russia).

Statistical data processing was performed using the Microsoft Excel (Microsoft Inc., USA) and GraphPad Prism 4.0 (GraphPad Software Inc., USA) software packages. The Kruskall–Wallis Test with the post-hoc Dunn's Multiple Comparison Test was used to assess the differences between the studied groups. The intergroup differences were considered significant with the p-value below 0.05 (significance level $\alpha = 0.05$).

RESULTS

Our findings show a significant increase in basal production of both IL6 and IL10 in all the studied groups relative to the comparison group of young adults, where the levels of these

Table. Criteria for dividing the studied groups into subgroups with successful and pathological aging

	Elderly age		Senile age		Centenarians	
Criteria	Successful aging	Pathological aging	Successful aging	Pathological aging	Successful aging	Pathological aging
CCI	2–3	4+	4–6	7+	4–8	9+
SSPB	11–12	1–10	9–12	0–8	8+	0–5
MMSE	28–30	below 28	28–30	below 28	24–30	below 24*

Note: * — based on the data [7].

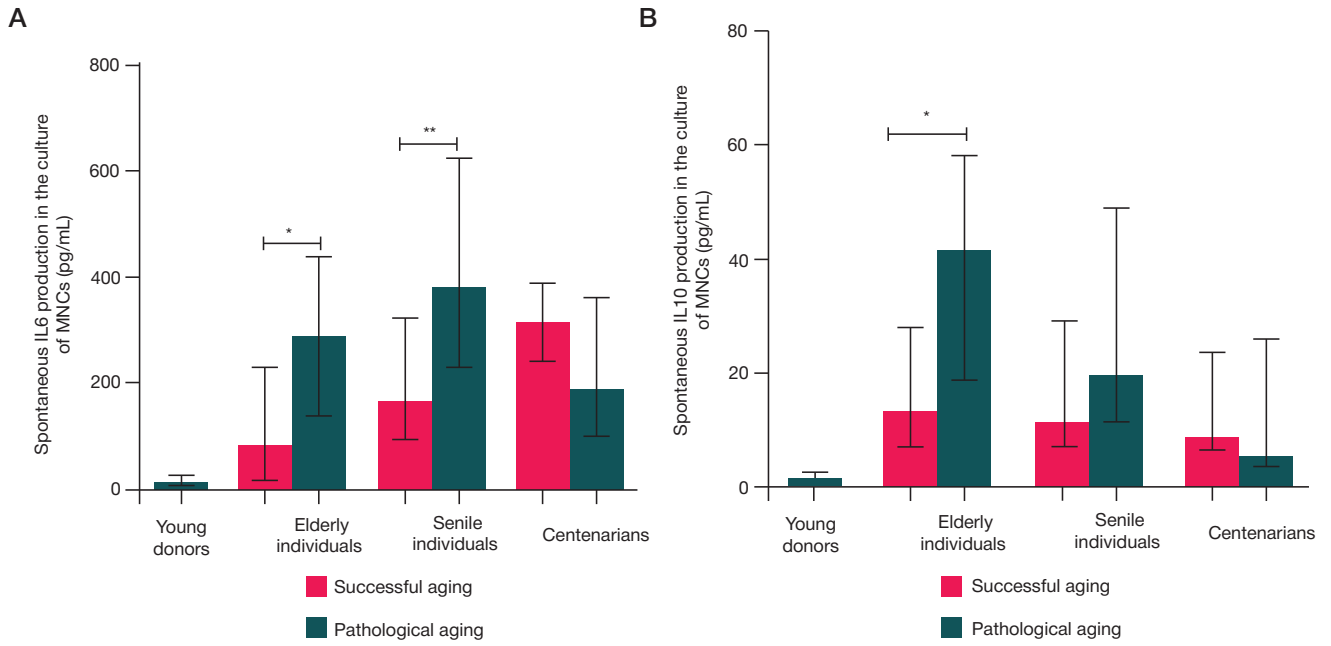

Fig. 1. Spontaneous IL6 **(A)** and IL10 **(B)** production in the culture of peripheral blood MNCs of elderly individuals, senile individuals, and centenarians with different aging phenotypes. The data are presented as the median (Me) and interquartile range, significant differences between aging phenotypes within the studied age groups: * — $p < 0.05$; ** — $p < 0.01$

cytokines were 12.5 [7.7–23.2] pg/mL and 1.4 [0.8–2.2] pg/mL, respectively (Fig. 1). Furthermore, the IL-6 levels that are elevated compared to the successful phenotype are also typical for elderly and senile individuals in the subgroups with pathological aging phenotype (Fig. 1A). Thus, in elderly individuals with the pathological aging phenotype, the levels of spontaneous IL6 production reached 289 [138–437] pg/mL, while that reported for the successful phenotype were 84.8 [19.4–232] pg/mL; in senile age, these were 377 [225–624] pg/mL for the pathological aging phenotype and 163 [97.3–319] pg/mL for the successful phenotype, respectively. No significant differences between phenotypes were reported for the group of centenarians. At the same time, the increase in the IL10 cytokine levels to 41.1 [18.5–58.1] pg/mL compared to the successful phenotype (13.2 [7.3–27.9] pg/mL) was typical for the pathological phenotype in the group of elderly individuals. Only the upward trend of IL10 levels was reported for the group of senile individuals (Fig. 1B).

In addition to assessment of spontaneous cytokine production by the peripheral blood MNCs, the cells were stimulated with the bacterial LPS. Such an approach can be considered as the method to assess potential pro- and anti-inflammatory activity of the innate immunity cells.

The stimulated IL6 production is increased in all groups, it shows the same general pattern of changes, as the spontaneous production (Fig. 2A).

However, the IL10 measurement results were more interesting (Fig. 2B). Thus, the subgroup of senile patients with successful aging showed the significantly ($p < 0.05$) higher levels (117.3 [61.3–318.2] pg/mL) compared to the

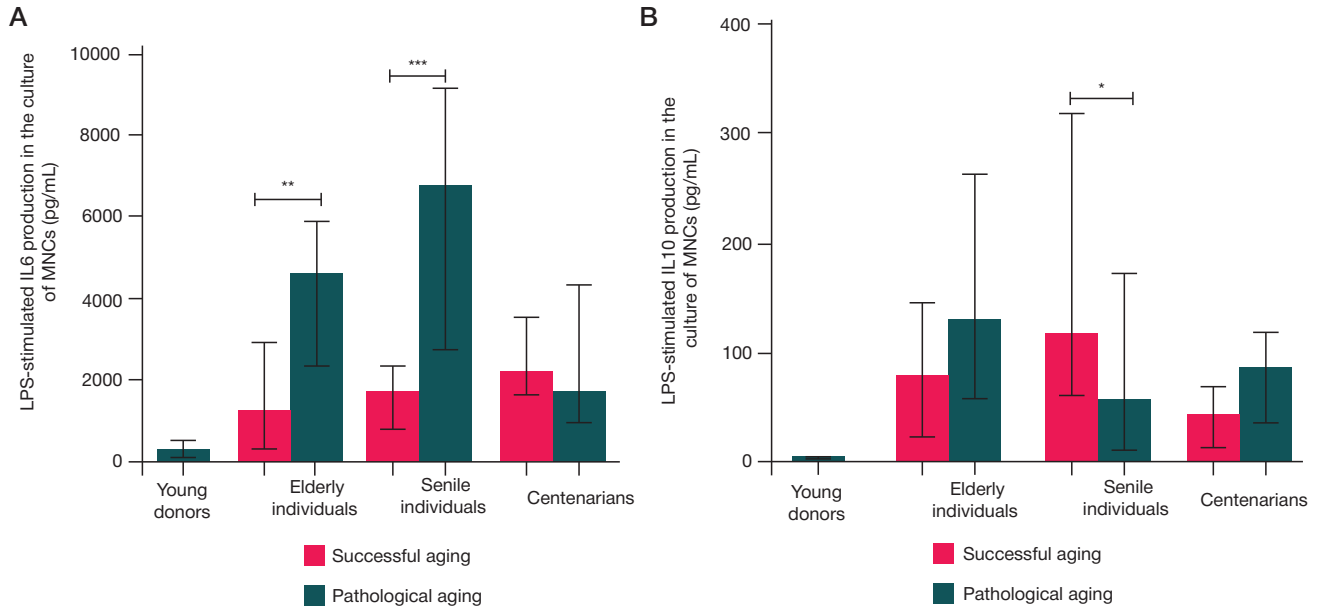

Fig. 2. LPS-induced IL6 **(A)** and IL10 **(B)** production in the culture of peripheral blood MNCs of elderly individuals, senile individuals, and centenarians with different aging phenotypes. The data are presented as the median (Me) and interquartile range, significant differences between aging phenotypes within the studied age groups: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$

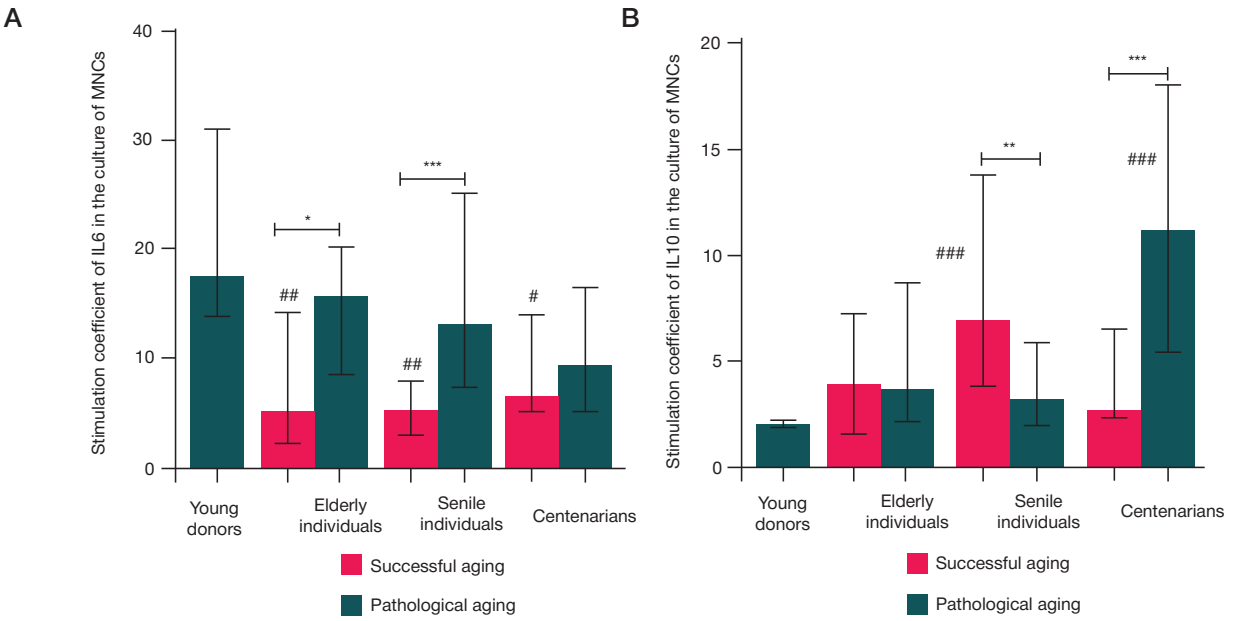

Fig. 3. Stimulation coefficients for IL6 **(A)** and IL10 **(B)** production in the culture of peripheral blood MNCs of elderly individuals, senile individuals, and centenarians with different aging phenotypes. The data are presented as the median (Me) and interquartile range, significant differences between aging phenotypes: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; significant differences relative to the comparison group (young donors): # — $p < 0.05$; ## — $p < 0.01$; ### — $p < 0.001$

subgroup with the pathological phenotype, where the values were 57.4 [10.8–172.3] pg/mL. No significant differences in IL10 production were revealed in the elderly patients and centenarians with different aging phenotypes.

For better interpretation of these data as an integral indicator of the spontaneous and stimulated cytokine production, the stimulation coefficient (SC) was used, representing the ratio of the stimulated cytokine production to its spontaneous production by peripheral blood MNCs. This coefficient can be considered as an indicator that the cells are ready to produce pro- and anti-inflammatory cytokines in response to PAMP and DAMP [9]. The increase in the SC of this or that cytokine can indicate the increased readiness to cytokine production, while the decrease can indicate the decreased readiness.

The SC for IL6 (SCIL-6) reaches its maximum in the comparison group — 17.6 [13.7–31.1] (Fig. 3A), which suggests high cell reactivity in young adulthood. Furthermore, successful aging phenotype demonstrates a significant SCIL-6 decrease with age, which reflects the immunoaging adaptive nature. In elderly individuals, the SCIL-6 values were 5.3 [2.2–14.3], in senile individuals these were 5.3 [3.01–7.8], in centenarians these were 6.5 [5.2–14.1]. Despite the fact that SCIL-6 demonstrates a downward trend in the elderly and senile individuals with the pathological phenotype, it shows no significant differences from that of young adults and remains significantly increased relative to the indicator reported for the successful phenotype. Centenarians represent a special group, where the presence of the age-associated disorder did not prevent longevity; the most prominent SCIL-6 decrease was reported for centenarians with both successful and pathological aging phenotypes. The SC for IL10 (SCIL-10) demonstrates the opposite changes (Fig. 3B). With age, the increase in this indicator was observed compared to the group of young adults, where it was 2.0 [1.9–2.2]. However, in elderly individuals, no significant differences compared to young adults or between the aging phenotypes are observed. Given high readiness for IL6 production by the cells in individuals of this age with pathological aging, this can be interpreted as imbalance in pro- and anti-inflammatory signals, which represents the sign of the developing inflammaging [10]. In senile age, such imbalance is much more prominent: multidirectional SC changes in the groups with successful and pathological aging are reported for IL6 and IL10. In the subgroup with successful aging, SCIL-10 was increased to 6.9 [3.8–13.8] vs. 3.3 [2.0–5.9] revealed in individuals with the pathological aging phenotype. In the group with pathological aging, SCIL-6 turned out to be increased — 13.2 [7.4–25.3] vs. 5.3 [3.01–7.8] in the subgroup with successful aging. In the group of centenarians, SCIL-10 was significantly increased in the subgroup with pathological aging (11.2 [5.4–18.1]), while in individuals with successful aging the value was 2.7 [2.3–6.5], it did not differ from the value of the comparison group.

Study limitation

This study did not consider the impact of gender on the findings, as well as the impact of the presence of certain age-associated disorders in patients of the studied groups.

DISCUSSION

Numerous studies of systemic cytokine levels show that elevated concentrations of pro-inflammatory cytokines, such as IL1b, TNF, IL18, and IL6, in blood are associated with geriatric syndromes, such as senile asthenia, sarcopenia, etc. [11], as well as with the more severe course of the age-associated disorder and in some cases with the risk of death [12]. Furthermore, the available data on anti-inflammatory cytokines are less informative. As for IL10, it is well known that the increase in IL10 levels is not associated with the presence of disorders or geriatric syndromes [13].

According to the research, elevated systemic levels of anti-inflammatory cytokines IL10 [14] and TGF-β [15] (compared to senile individuals) are typical for centenarians; our previous findings are also in line with these data [2]. However, these data are hardly applicable for the elderly and senile age groups, since the levels of anti-inflammatory cytokines turn out to be low and show no relationship with the age-associated disorder.

A slow increase in pro-inflammatory cytokine levels that is asymptomatic and referred to as low-grade inflammation is

typical for inflammaging. At the same time, the development of infectious disease or exacerbation of chronic non-communicable disease results in the fact that the inflammatory response reaches the clinically significant level. However, the immune system reactivity is commonly not assessed in such situations. Assessment of the IL10 and IL6 production in vitro can be considered as assessment of such reactivity.

The increase in spontaneous IL10 and IL6 production in MNC cultures *in vitro* in individuals of older age groups relative to young donors can be interpreted as the fact of pre-stimulation of cells at the organism level resulting from the increase in the PAMP and DAMP circulating molecular patterns [16]. This is in line with the available literature data. In particular, it has been shown that both basal and stimulated TNF production by the peripheral blood cells increases with age [17]. Such stimulation is more prominent in elderly and senile individuals with the pathological aging phenotype. In the group of elderly individuals, a significant increase in IL10 levels also attracts attention, which can be considered as a compensatory response that inhibits pro-inflammatory activity. No significant differences in spontaneous cytokine production have been revealed in the group of centenarians with different phenotypes.

LPS stimulation of cells leads to the increased production of both IL6 and IL10 in all age groups, exceeding the cytokine levels of young individuals under the same conditions. However, the pathological aging phenotype is characterized by higher IL6 compared to the successful phenotype even in elderly individuals, which suggests the onset of inflammaging and setting an unfavorable trajectory of the aging process [18]. In senile individuals with the pathological phenotype, these manifestations are complemented by the decreased stimulated IL10 production relative to the successful aging phenotype.

The analysis of the SC as an integral indicator reflecting cell reactivity during cytokine production shows that with the successful aging phenotype all the older age groups, including centenarians, show the SCIL-6 decrease compared to young individuals. This can be considered as a favorable adaptive process that accompanies aging and shows that, despite the general increase in basal IL6 production, the readiness for further pro-inflammatory activity is limited, which inhibits inflammaging. While the lack of reactivity or insufficient decrease in reactivity in relation to IL6 production with age suggests unfavorable course of aging. Furthermore, SCIL-10, indicating readiness for IL10 production, in contrast, shows an upward trend with age. Despite the fact that no significant differences in SCIL-10 between aging phenotypes and compared to young adults have been reported for elderly people; in senile age, elevated SCIL-10 indicates the successful aging phenotype.

It has been noted that centenarians represent a special group, where we see a significant SCIL-10 increase specifically in the group with pathological aging, which can play a role of counterweight to the inflammaging processes in this group being one of possible factors associated with the longevity of these people [4]. Thus, we can say that a successful aging trajectory looks like the decreased readiness to IL6 production and increased readiness to IL10 production. Similar data were obtained for the long-living model rats, in which the increase in basal and stimulated IL10 expression by peritoneal macrophages was revealed, while similar IL6 levels and levels of other pro-inflammatory cytokines were lower, than in senile animals of control lineages [19].

Senile age is likely to be a critical period, when imbalance of pro- and anti-inflammatory factors, that has emerged in the elderly, results in severe manifestations of the pro-inflammatory aging phenotype [20, 21], such as rapid development of the age-associated disorder and aging manifestations affecting both physical performance and cognitive functions.

Despite the fact that the increased anti-inflammatory activity, specifically that related to IL10, can be a risk factor of both infectious diseases and cancer, it is of positive nature, since it is an inflammaging inhibitor. Thus, pro- and anti-inflammatory cytokines demonstrate their dual nature, serving as both protective and pathogenetic factors. Inflammation is a key component of immune responses to a pathogen. However, excess inflammation can result in numerous non-communicable diseases and increase the associated mortality rate. In terms of evolution, the immune system is optimized to fight infections in young adulthood, when pro-inflammatory responses are critical for survival. However, in the later age period excess inflammation becomes a risk factor of age-associated disorders, while inflammation limitation involving the anti-inflammatory cytokine system can contribute to longevity.

CONCLUSIONS

The aging process is accompanied by various changes in the body, including the immune system alterations. The immune system aging and inflammaging represent two inseparable processes inevitably launched in the body with age. Depending on external environmental factors and genetic predisposition, these shape the course of senility. If the body continues to adequately respond to external and internal danger signals (PAMP and DAMP) during aging and the associated changes in the innate immune system, then we can talk about the successful aging type, which in turn is accompanied by the anti-inflammatory status predominance, which compensates for excessively enhanced inflammatory activity. In the case where the threshold of adequate response is overcome, and the body responds with excessive production of pro-inflammatory mediators, without compensating for this with anti-inflammatory components, a pathological type of aging develops. We have developed an approach to the aging phenotype assessment based on determination of the stimulation coefficient representing the ratio of the stimulated cytokine production by peripheral blood MNCs to the spontaneous production. This coefficient can be considered as an indicator of inflammaging. The decrease in SC of IL6 with the increase in SC of IL10 was reported in the elderly and senile individuals with the successful aging phenotype. In the group of centenarians with the pathological aging phenotype, a significantly increased SC of IL10 was reported, which suggests a large compensatory anti-inflammatory reserve being the factor of survival and longevity in polymorbid individuals.

Functional assessment of the innate immunity cell pro-/anti-inflammatory activity can provide the basis for the personalized approach to prevention of age-associated disorders focused on maintaining adequate conditions of the external and internal environment, careful inflammation suppression, including pharmacological suppression, and shapes the possibility of active longevity.

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