REGULATORY SUPPRESSOR Treg CELLS IN IMMUNOPATHOGENESIS OF RADIATION-INDUCED PULMONARY FIBROSIS

A.F. Tsyb Medical Radiological Research Center – Branch of the Federal State Budget Institution "National Medical Research Center of Radiology" of the Health Ministry of the Russian Federation, Obninsk, Russia

Kuzmina E.G., Mushkarina T.Yu., Zatsarenko S.V., Kursova L.V., Pasov V.V.

Introduction: Study of the action of suppressor T regulatory cells (Treg) on immune status after treatment oncology diseases should receive a high priority [1]. Identification of their influence on the immune system will offer deeper insights of the pathogenesis of fibrosis.

The objective of research was to evaluate regulatory functions of Treg cells in radiation-induced lung injuries.

Materials and methods. A total of 45 patients with radiation-induced pulmonary fibrosis were examined. Their medical history contained information about combination treatment for breast cancer, lung cancer and Hodgkin lymphoma including radiotherapy with total doses of 40-70 Gy.

We evaluated T cells and their functional state [CD3, CD4, CD8; activated CD3+HLA-DR+; regulatory T cells (Treg) including CD45+CD4+CD25+CD127–; naive and memory T cells (CD4+CD45RA+CD45RO–/ CD4+CD45RA-CD45RO+); apoptosis of CD3+CD95+, CD4+CD95+; proliferation according to lymphocyte blast transformation]. Furthermore, B cells (CD19, concentration of Ig M, G, A classes); natural killer (NK) cells (CD16); phagocytosis of Staphylococcus aureus was evaluated too. A group of 50 healthy persons served as a control. The factorial and correlation analysis was performed using STATISTICA 8.0 software.

Results

Suppression of T cell-mediated immunity prevailed (Fig.1). There was a decrease in both the percentage and absolute number of T cells (mainly naive CD4+T cells) involved in providing anti-infectious and anti-tumor immunity. The proliferative potential of T-lymphocytes in the lymphocyte blast transformation (BT) reaction was reduced too (Fig1A). Enrichment of T cell-specific immune memory was suggestive of the encounter with cells bearing viral and tumor-associated antigens. Increased levels of activated T cells and percentages of B-lymphocytes, higher serum immunoglobulin (IgG) concentrations and more intensive phagocytosis pointed to the predominance of humoral responses reflecting an elevated level of the antigenic components in blood circulation.

Patients with pulmonary fibrosis showed a higher percentage of Treg (Fig1B). Spearman's test revealed multi-directional correlations between the percentage or the number of Treg and other parameters of immunity (Tab.1). The absolute number of Treg correlated directly with the numbers of T helper cells and cytotoxic T lymphocytes, their death by apoptosis as well as with the numbers of lymphocytes and memory T helper cells. Increased percentages correlated with decreased numbers of T helper cells, naive T lymphocytes and T cells undergoing apoptosis as well as with T lymphocyte proliferation. Direct correlation was noted between the percentage of Treg and activated T cells. There was an inverse relationship between their increased numbers and decreased numbers of activated and naive cells of the lymphocyte pool and reduced percentage of NK cells.

Conclusion. Our results suggest that it is necessary to update treatment plans for lung damage after combination therapy. Important concepts for the prevention of lung injuries include new clinical approaches aimed at restoring immunity and protecting tissues from immunosuppressive factors such as elimination of excess Tregs or influence on the mechanisms of their function [2]. It may promote immune recovery, attenuate inflammatory manifestations and prevent pulmonary fibrosis.

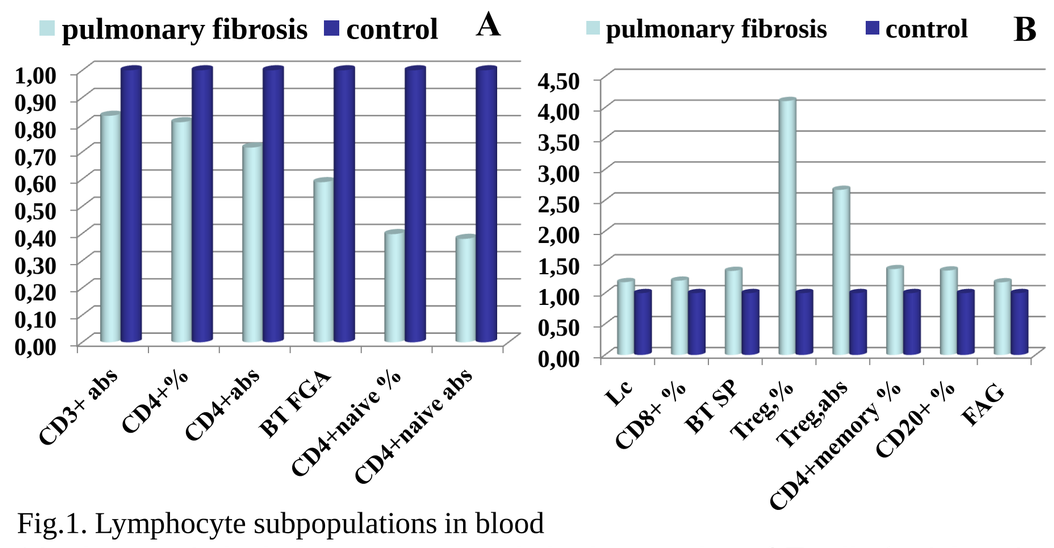

Fig.1. Lymphocyte subpopulations in blood
1A- decrease in both the percentage and absolute number of T cells (mainly naive CD4+T cells), lymphocyte blast transformation (BT PHA)
1B - increased levels of leucocytes, spontaneous lymphocyte blast transformation (BT Sp) percentage and number of Treg, activated T cells, T cell-specific immune memory cells, percentages of B lymphocytes and phagocytosis.

Differences are statistically significant between parameters of pulmonary fibrosis and control , $p<0,05$.

Tab.1. Spearman's test revealed multi-directional correlations between the number or the percentage of Tregs and other parameters of immunity.

	Treg,abs	Treg,%
Lf abs	0,6	-0,4
CD3+ abs	0,6	-0,4
CD4+%	0,5	-0,5
CD4+abs	0,7	-0,5
CD8+abs	0,4	-0,2
CD4+/CD8+	0,3	-0,4
CD3+CD95+abs	0,5	-0,4
CD4+CD95+abs	0,7	-0,5
CD45RO+CD45RA- %	0,5	0,1
CD45RO+CD45RA- abs	0,7	-0,3
CD45RA+CD45R0-abs	0,3	-0,5
CD4+CD45R0+CD45RA-abs	0,8	-0,5
CD4+CD45RA+CD45R0+abs	0,1	-0,4
CD3+HLA-DR+ %	-0,3	0,4
CD45RA+CD45R0- %	-0,6	0,0

References

1. Schaue D, Xie MW, Ratikan JA, McBride WH. Regulatory T cells in radiotherapeutic responses. Front Oncol. 2012;2:90.
2.Whiteside TL. Disarming suppressor cells to improve immunotherapy. Cancer Immunol Immunother. 2012;61:283–8.

e-mail: kuzmina_e_g@mail.ru