COMPLEMENT C3 DEFICIENCY INCREASES THE ANTITUMOR IMMUNITY OF NK CELLS AND CONTROLS TUMOR GROWTH


Background Natural killer cells play an important role in controlling tumor growth. On the other hand, the complement system is known for its protective function in infection and for maintaining cellular homeostasis. It is reported that the complement system promotes tumor growth and metastasis. However, the role of complement and its importance in the anti-tumor function of NK cells is not clearly understood.

Methods Mouse melanoma cell B16F10 was subcutaneously injected in C57BL/6 mice or C3-/- mice, and the growth of the tumor was monitored. The cellular phenotyping of immune cells in the tumor and secondary lymphoid tissues were analyzed using flow cytometry.

Results The transplantation of B16F10 cells in the C3-/- mice showed a significantly reduced tumor growth compared to wild-type mice. Immunohistological analysis of tumor showed increased infiltration of NK cells and CD8 T cells in the C3-/- mice as compared to C3+/+ mice. Under the homeostatic condition, analysis of spleen and lymph nodes of C3-/- and C3+/+ mice did not show any change in either the frequency or the absolute number of total CD4 T cells, CD8 T cells, NK cells, and NKT cells. However, CD4+ T cells and CD8+ T cells from C3-/- mice secreted significantly higher IFN-g than C3+/+ mice and the splenic NK cells from C3-/- mice showed a significantly increased cytotoxic activity compared to C3+/+ mice. Further, hepatic NK cells in the C3-/- mice showed significantly lower NKG2A inhibitory receptors, resulting in reduced NKG2D to NKG2A ratio (activating/inhibitory ratio) of molecules per NK cell compared to wild-type NK cells. As expected, NK cells isolated from tumor-bearing C3-/- mice showed a robust cytotoxic activity compared to the tumor-bearing C3+/+ mice. Interestingly, C3-/- NK cells showed increased secretion of pro-inflammatory cytokines such as GM-CSF and IFN-g when re-stimulated with IL-2, IL-15, or IL-18 compared to C3+/+ NK cells. Depleting NK cells in C3-/- mice with anti-NK1.1 mAb significantly prevented the reduction of tumor growth as compared to isotype control IgG mAb.

Conclusions Our data suggest that complement C3 deficiency alters the effector and cytotoxic function of NK cells, and thereby deficiency of C3 promotes anti-tumor immunity and controls tumor growth. Our data suggest that interfering with the complement system gives a new therapeutic advantage in controlling tumor growth.

Acknowledgements PP received a Senior Research Fellowship from the Department of Biotechnology, Government of India. GL received grants (EMR/2016/007108 and DST/SJF/LSA-01/2017-18) from the Science and Engineering Research Board, Department of Science and Technology, Ministry of Science and Technology, Government of India. A.S. is a J. C. Bose National Fellow. His laboratory is supported by project grant BT/PR28506/MED/29/1307/2018 from the Department of Biotechnology, New Delhi, India.