ROLE OF IRF-8 IN THE INTERFACE OF MELANOMA TUMOR CELL-IMMUNE SYSTEM INTERACTION.

Fabrizio Mattei, Giovanna Schiavoni, Massimo Spada, Francesca Spadaro and Lucia Gabriele

Department of Cell Biology and Neurosciences, Istituto Superiore di Sanità, Rome, Italy.

ABSTRACT

Interferon regulatory factor 8 (IRF-8) is essential for differentiation and function of myeloid dendritic cell (DC) populations and thus for the induction of competent immune responses. Moreover, IRF-8 acts as a tumor suppressor gene in different types of malignancies. Recent evidence suggested that DCs are critical players in the immunosurveillance against tumors and that tumor-infiltrating DC (TIDC) may affect the development of antitumor responses. However, the mechanisms underlying DC/human cell interaction and the combination of different DC subtypes with the tumor cells remains elusive. Here, we investigated the role of IRF-8 in affecting immune response against melanomas. To this end, we transplanted B16-F10 metastatic melanoma cells into immunocompetent (WT) and IRF-8-deficient (IRF-8 KO) mice. We found that melanoma expansion rapidly in IRF-8 KO mice whereas its growth was more restrained in WT animals. In fact, IRF-8 KO mice exhibited remarkably higher tumor growth, in terms of mean volume and diameter, which resulted in reduced survival rates with respect to WT control mice. We examined the immune cells infiltrating melanomas in WT and IRF-8 KO mice and found severe reduction of TIDC in IRF-8 KO mice, resulting those subsets that are present in normal number in these mice, namely CD11b+CD11c+ DCs, with respect to WT mice, which supported sustained infiltration of the DC subset. To test whether the expansion of IRF-8 KO melanomas in rats could be modulated during tumor growth; we examined the levels of IRF-8 mRNA in melanoma cells transplanted into bone marrow negative WT and IRF-8 KO mice in different stages, while the tumor size was approximately equal. In this scenario, IRF-8 was highly expressed in melanomas grown in WT hosts in each tumor stage analyzed, whereas it was undetectable in tumors developed in IRF-8 KO mice. These results reveal a critical role of IRF-8 in controlling melanoma growth and suggest that IRF-8-mediated antitumor activity is the result of a coordinated action between DC-mediated immune response and the tumor suppressor function of IRF-8. Our data suggest that these two functions may be highly connected and open new perspectives in understanding the complex mechanisms of tumor cell-immune system interactions.

The transcription factor IRF-8 is a key regulator of hematopoietic stem cells and plays a critical role in the development and maturation of mouse plasmacytoid DCs, CD8+ T cells and DC subsets. IRF-8-KO mice exhibit reduced immune responses towards various pathogens.

Mice in immune system
- Transcription factor binding the Interferon Regulatory Factors (IRF) family
- Regulation of immune responses against pathogens
- Growth of hematopoietic cells
- Development and maturation of mouse plasmacytoid DCs, CD8+ T cells and DC subsets
- IRF-8-KO mice exhibit reduced immune responses towards various pathogens.

Mice in tumor development
- IRF-8 deficiency results in the development of melanomas
- Suppression of long-term proliferation by expression of IRF-8 after transplantation of a melanoma
- IRF-8 loss in mice results in increased melanoma growth.

The transcriptions factor IRF-8 rules in immunity and tumor.

REFERENCES

Main body IRF-8 expression induces faster growth of transplanted B16 melanoma, which associates with reduced tumor inhibition by CD4+ T cells, CD8+ T lymphocytes and with down-regulation of IRF-8 expression in B16 tumors.

Restoration of IRF-8 expression by 5-Aza-dC treatment led to a transient arrest of melanoma growth in IRF-8 KO hosts.

IRF-8 may represent a key factor regulating the interplay between melanoma tumor growth and host immune system.

SUMMARY AND CONCLUSIONS

- IRF-8 may represent a key factor regulating the interplay between melanoma tumor growth and host immune system.
- Restoration of IRF-8 expression by 5-Aza-dC treatment led to a transient arrest of melanoma growth in IRF-8 KO hosts.
- IRF-8 expression induces faster growth of transplanted B16 melanoma, which associates with reduced tumor inhibition by CD4+ T cells, CD8+ T lymphocytes and with down-regulation of IRF-8 expression in B16 tumors.