Cancer Immunity (15 December 2008) Vol. 8 Suppl.2, p. 6

CANCER
IMMUNITY
Meeting Abstract

Is an anticancer immune response mandatory for therapeutic success?

Laurence Zitvogel[1,2,3,4*], Lionel Apetoh[1,3,4], François Ghiringhelli[1,2,3], Fabrice André[3], Antoine Tesniere[3,4,5] and Guido Kroemer[3,4,5]

[1]*INSERM, U805, Villejuif, France*
[2]*CIC BT507, Villejuif, France*
[3]*Institut Gustave Roussy, Villejuif, France*
[4]*Faculté Paris Sud-Université Paris 11, Kremlin-Bicêtre, France*
[5]*INSERM, U848, Villejuif, France*
[*]*Presenting author*

Abstract

The question as to whether and to which extent immunosurveillance controls and shapes the development of human cancers has been the subject of recent reviews. One important question concerns the impact of conventional anticancer chemotherapy on the relationship between the tumor and the immune system. Therapy, which is applied during the escape phase, not only affects the tumor; it also modulates the relationship between the tumor and the immune system. Thus, chemotherapy can, by simply reducing the tumor mass ("debulking"), reduce its immunosuppressive properties. By enforcing the selection of chemotherapy resistant tumor cells and by inducing additional mutations (chemotherapy often involves mutagenic agents), therapy can induce the expression of new tumor antigens. Chemotherapy can cause immunogenic cancer cell stress or death and hence mediate some kind of cancer vaccination effect. Furthermore, chemotherapy can stimulate the immune system, either by a direct effect on immune effectors or regulatory mechanisms or indirectly, by causing lymphopenia followed by homeostatic proliferation of immune effectors that may be particularly active in the anticancer response. The combination of these effects may reset the relationship between the tumor and the immune system from the latest stage (escape) to a preceding state (elimination or equilibrium).

Thus, we recently reported that oxaliplatinum, anthracyclines and X Rays specifically induce antitumor immune responses that result from immunogenic cancer cell death. This anticancer immune response then helps to eliminate residual cancer cells (that failed to be killed by chemotherapy) or maintains micrometastases in a stage of dormancy. We have investigated the molecular pathways involved in the immunogenicity of cell death (triggered by cytotoxic compounds) and delineated certain components dictating the cross-talk between dying tumor cells and dendritic cells. We have reported that the rapid exposure of calreticulin to the cell membrane (1), followed by the exodus of the nuclear high mobility group box1 protein (2) and other new molecules (3) all contributed to mobilize dendritic cells for T cell activation in tumor-bearing hosts. This work has several clinical implementations. First, the description of single nucleotide polymorphisms located in genes encoding immune functions and receptors involved in the immunogenicity of cell death may have impact on the success of some therapeutic regimen. Compensating genetic defects in the signaling pathways dictating the immunogenicity of cell death may be a key strategy to transform non responses into objective clinical benefit. Second, we will also discuss the rationale of clinical trials to evaluate and eventually increase the contribution of anti-tumor immune responses to the therapeutic management of neoplasia.

References

1. Obeid M, Tesniere A, Ghiringhelli F, Fimia GM, Apetoh L, Perfettini JL, Castedo M, Mignot G, Panaretakis T, Casares N, Métivier D, Larochette N, van Endert P, Ciccosanti F, Piacentini M, Zitvogel L, Kroemer G. Calreticulin exposure dictates the immunogenicity of cancer cell death. *Nat Med* 2007; **13:** 54-61. (PMID: 17187072)

2. Apetoh L, Ghiringhelli F, Tesniere A, Obeid M, Ortiz C, Criollo A, Mignot G, Maiuri MC, Ullrich E, Saulnier P, Yang H, Amigorena S, Ryffel B, Barrat FJ, Saftig P, Levi F, Lidereau R, Nogues C, Mira JP, Chompret A, Joulin V, Clavel-Chapelon F, Bourhis J, André F, Delaloge S, Tursz T, Kroemer G, Zitvogel L. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. *Nat Med* 2007; **13:** 1050-1059. (PMID: 17704786)

3. Ghiringhelli F *et al.* Manuscript in revision.