Cancer is not just a disease of a tissue: It is a host disease
How to reanimate host defense against tumors using conventional therapeutics of cancer?

Le cancer n’est pas seulement une maladie d’un tissu mais aussi de l’hôte : comment donc réactiver les défenses de l’hôte contre une tumeur tout en utilisant des traitements conventionnels du cancer?

L. Apetoh a,b,c, F. Ghiringhelli a,b,c, A. Tesniere a,b,c, M. Obeid a,b,d, G. Mignot a,b,c, E. Ullrich a,b,c, G. Kroemer a,b,d, L. Zitvogel a,b,c,*

a Institut Gustave-Roussy, 39, rue Camille-Desmoulins, 94805 Villejuif, France
b Faculté Paris-Sud, université Paris-XI, institut Gustave-Roussy, 39, rue Camille-Desmoulins, 94805 Villejuif, France
*c* Inserm, U805, institut Gustave-Roussy, 39, rue Camille-Desmoulins, 94805 Villejuif, France
d Inserm, Unit “Apoptosis, Cancer and Immunity”, institut Gustave-Roussy, 39, rue Camille-Desmoulins, 94805 Villejuif, France

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Apoptosis was believed to be a silent cell death modality that fails to trigger innate or adaptive immune responses. Millions of cells die every day within our body through apoptosis, without eliciting an immune response, suggesting that apoptosis is a non-immunogenic cell death modality. By contrast, necrosis, an unprogrammed form of cell death, leads to the release of cellular content into the extracellular space, which possibly sets off an immune response. This sharp dichotomy regarding the immunogenicity of apoptosis and necrosis was questioned by some studies that pointed out that rather than the type of cell death, the tumor cells themselves or the nature of the death-inducing stimulus would influence the immunogenicity of dying cells.

Nonetheless, programmed cell death contributes to the onset of an adaptive immune response either directly or indirectly, during viral or bacterial infection or anticancer chemotherapy [1]. Toll-like receptors (TLR) recognize molecules derived from microbes, as well as endogenous danger signals possessing similar chemical structures. We describe now a previously unrecognized pathway for activation of tumor antigen-specific adaptive immune responses that, in a murine model, is dependent on TLR4 signalling and the high mobility group box 1 (HMGB1) alarmin secreted by dying tumor cells. During chemo- (anthracyclines, oxaliplatin) or radiotherapy (x-rays), conventional dendritic cells (DC) require TLR4/Myd88 signaling for efficient processing and cross-presentation of tumor antigens. Pharmacological agents such as lysosomotropic drugs that interfere with the fusion between endosomes and lysosomes can convert TLR4 deficient DC into efficient antigen presenting cells [2].

A genetic polymorphism has been largely described in the TLR4 gene (Asp299Gly). Breast cancer patients carrying a TLR4 loss-of-function allele manifest an earlier relapse after radio- and chemotherapy than patients carrying the normal TLR4 allele. These results delineate a clinically relevant immunoadjuvant pathway triggered by tumor cell death [2].

Challenging the notion that chemotherapy or radiotherapy negatively affects the immune system, accumulating evidence (from the 1970s to now) indicate that cell death can induce an immunological cascade that will contribute to the antitumor effects of conventional cytotoxic agents. Anthracyclines are key intercalating agents which also promotes the translocation of calreticulin from the endoplasmic reticulum to the plasma membrane, triggering the efficient uptake of dying tumor cells by dendritic cells and the immunogenicity of cell death [3]. Besides the notion that cytotoxic agents can elicit specific cellular responses that render tumor cell death immunogenic, other immunological side-effects associated with a beneficial clinical outcome have been described [4]. Alkylating agents and fludarabine, by inducing transient lymphodepletion, can reset memory T-cell responses. Metronomic cyclophosphamide, by subverting regulatory T-cells and immunosuppressive mechanisms, can...
ameliorate T- and NK-cell responses [5]. ATRA (retinoic acid) by restoring the maturing function of myeloid DC, will favour T-cell responses. Flavanoids positively influence the chemotraction of effectors to tumor beds. Imatinib mesylate enhances the DC-mediated NK-cell activation which is instrumental for the control of NK sensitive tumors (such as GIST), [6,7]. x-rays and 5-FU can sensitize tumor cells to lysis by CTLs.

Altogether, cytotoxic compounds used in the clinical armamentarium can not only target tumor cells but also boost the host defenses against cancer and contribute to the control of the residual disease. Our challenge will be to propose optimal and tailored management of cancer patients by combining immunotherapy with chemotherapy or Ab-directed compounds.

Further reading


References


