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On the role of dendritic cells versus other cells in inducing protective CD8+ T cell responses

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Dendritic cells (and/or macrophages) are key transporters of antigen from extra-lymphatic tissue to secondary lymphatic organs. The phagocytized antigen is presented via MHC class II but not via class I, except for infections by intracellular viruses, bacteria, etc. (1–4).

Class II-negative cells (e.g., fibroblasts) that get drained to secondary lymphatic organs (including spleen) induce MHC class I restricted CD8 T cells' cell responses as efficiently as dendritic cells (5–7).

So called crosspresentation is at least 10^5 times less efficient than direct presentation and therefore is practically not achievable under physiological conditions (5–8).

If antigen accumulates in the endoplasmic (ER) reticulum because of transport problems, crosspresentation on to MHC class I can be demonstrated. This requires gigantic amounts of antigen accumulation in the ER, but this process has so far been difficult to quantitate in comparison to direct presentation (9).

Positive demonstration of crosspresentation in experiments is sometimes based on use of excessive amounts of protein antigen (e.g., OVA) and/or the use of unphysiological (i.e., much too sensitive) detection method, e.g., using very high frequencies of transgenic T cells (e.g., OVA-specific tgCD8$^+$ T cells). In some experiments, virus inactivation is not controlled properly, permitting abortive (but not virus productive) infections that seemingly suggest crosspresentation instead of direct presentation [e.g., Ref. (8)].

An insulin-producing allogeneic cell graft strictly transplanted under the kidney capsule is accepted for more than >200 days by the host, but is promptly rejected if at the time of transplantation, or a few days later, the same cells are also given i.p. or i.v. (10) Once accepted, the allogeneic strictly peripheral cell graft is highly resistant to rejection by a transplanted corresponding allogeneic skin graft (or dendritic cells). This skin graft is rejected in a primary fashion, signaling absence of direct or indirect priming by the original allogeneic cell graft indicating absence of priming by the original cell graft. This prompt skin rejection does not cause rejection of the insulin-producing cell graft (10).

A strictly extralymphatic (7) tumor expressing a very strong and defined viral antigen (similar to insulin-producing self-beta-cells or allogeneic islet cells (10–12) can grow successfully to become lethal tumors. This depends on the condition that at the time of syngeneic tumor cell transplantation no (or too few) tumor cells escape/or drain to secondary lymphatic organs (7). This potentially early direct immunization is distinct from the late process of metastasis to secondary lymphatic organs that very often represent immune escape of tumor cells (e.g., MHC mutants, mutations of the T cell epitope, barrier formation by fibrin, coagulation, etc.)

DISCUSSION

DC transport antigen best to secondary lymphatic organs but only in an MHC class II associated fashion except of course if the DC is productively or abortively infected. The localization in or strictly outside of secondary lymphatic organs determines if and whether a CD8$^+$ T cell immune response is induced or not. Crosspresentation of antigen to MHC class I by DC or macrophages is an experimental artifact due to overdosage or uncontrolled new cell internal synthesis. Pure crosspresentation is so inefficient, that it is largely impractical for application and therapeutic use against solid peripheral tumors.

REFERENCES

1. Banchereau J, Steinman RM. Dendritic cells and the control of antigen immunity. *Nature* (1998) **392**:245–52. doi:10.1038/32588
2. Ludewig B, Odermatt B, Landmann S, Hengartner H, Zinkernagel RM. Dendritic cells induce autoimmune diabetes and maintain disease via De novo formation of local lymphoid tissue. *J Exp Med* (1998) **188**:1493–501. doi:10.1084/jem.188.8.1493
3. Ludewig B, Maloy KJ, Lopez-Macias C, Odermatt B, Hengartner H, Zinkernagel RM. Induction of optimal anti-viral neutralizing B cell responses by dendritic cells requires transport and release of virus particles in secondary lymphoid organs. *Eur J Immunol* (2000) **30**:185–96. doi:10.1002/1521-4141(200001)30:1<185::AID-IMMU185>3.0.CO;2-L
4. Ludewig B, Ochsenbein AF, Odermatt B, Paulin D, Hengartner H, Zinkernagel RM. Immunotherapy with dendritic cells directed against tumor antigens shared with normal host cells results in severe autoimmune disease. *J Exp Med* (2000) **191**:795–804. doi:10.1084/jem.191.5.795
5. Kündig TM, Bachmann MF, DiPaolo C, Simard JJ, Battegay M, Lother H, et al. Fibroblasts as efficient antigen-presenting cells in lymphoid organs. *Science* (1995) **268**:1343–7. doi:10.1126/science.7761853
6. Zinkernagel RM. On cross-priming of MHC class I-specific CTL: rule or exception? *Eur J Immunol* (2002) **32**:2385–92. doi:10.1002/1521-4141(200209)32:9<2385::AID-IMMU2385>3.0.CO;2-V
7. Ochsenbein AF, Sierro S, Odermatt B, Pericin M, Karrer U, Hermans J, et al. Roles of tumour localization, second signals and cross priming in cytotoxic T cell induction. *Nature* (2001) **411**:1058–64. doi:10.1038/35082583

8. Freigang S, Egger D, Bienz K, Hengartner H, Zinkernagel RM. Endogenous neosynthesis vs. cross-presentation of viral antigens for cytotoxic T cell priming. *Proc Natl Acad Sci U S A* (2003) **100**:13477–82. doi:10.1073/pnas.1835685100
9. Freigang S, Eschli B, Harris N, Geuking M, Quirin K, Schrempf S, et al. A lymphocytic choriomeningitis virus glycoprotein variant that is retained in the endoplasmic reticulum efficiently cross-primes CD8(+) T cell responses. *Proc Natl Acad Sci U S A* (2007) **104**:13426–31. doi:10.1073/pnas.0704423104
10. Pericin M, Althage A, Freigang S, Hengartner H, Rolland E, Dupraz P, et al. Allogeneic beta-islet cells correct diabetes and resist immune rejection. *Proc Natl Acad Sci U S A* (2002) **99**:8203–6. doi:10.1073/pnas.122241299
11. Ohashi PS, Oehen S, Buerki K, Pircher HP, Ohashi CT, Odermatt B, et al. Ablation of "tolerance" and induction of diabetes by virus infection in viral antigen transgenic mice. *Cell* (1991) **65**:305–17. doi:10.1016/0092-8674(91)90164-T
12. Ochsenbein AF, Klenerman P, Karrer U, Ludewig B, Pericin M, Hengartner H, et al. Immune surveillance against a solid tumor fails because of immunological ignorance. *Proc Natl Acad Sci U S A* (1999) **96**:2233–8. doi:10.1073/pnas.96.5.2233

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