Mechanisms by Which Tumor Cells Evade Immune Surveillance: Loss of T Cell Recognition

- Antigen loss variants
- Loss of TAPs and other molecules involved in antigen processing
- Down modulation of HLA Class I and II molecules

Mechanisms by Which Tumor Cells Evade Immune Surveillance: Intrinsic Resistance to Apoptosis

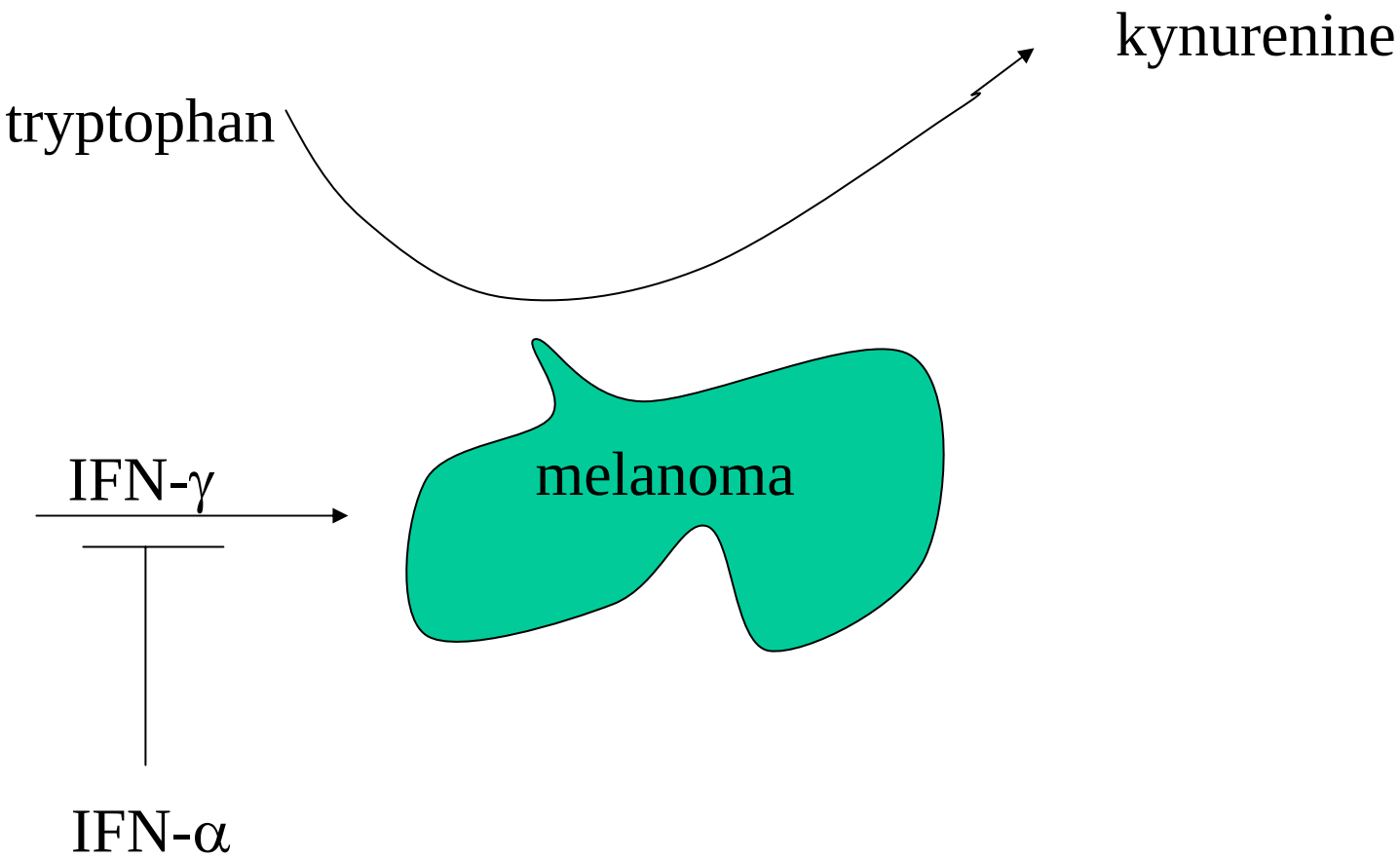
- Overexpression of bcl-2, bcl-x_L, FLIP, survivin, other IAPs
- Loss of fas, other DRs
- PI-9 (Godal *et al*, SBT 2004)

Accumulation of Tregs

- 17% of $CD4^+$ TIL in a murine breast carcinoma are $CD25^+$ (many also CTLA-4^+ also) – 3-fold the percentage among $CD4^+$ splenocytes.
- As much as 1/3 of $CD4^+$ TIL are $CD25^+$ early in the development of a tumor (Dang *et al*, SBT 2004)

Metabolic Mechanisms of Immunosuppression: Amino Acid Depletion

- Arginine depletion (Ochoa *et al*, SBT 2003) with down modulation of TCR-ζ, NF-κB, $p56^{lck}$
- Tryptophan – indoleamine 2,3-dioxygenase (IDO pathway)



Induction of IDO by IFN-γ (Redlitz-Tountas *et al*, SBT 2004)

Immune Inactivation by Tumor-Derived Cytokines: TGF-β

- Production of TGF-β by gastric carcinoma correlated with LN metastases, reduced infiltration by $S100^{+}$ DC, and reduced 5 yr survival (Iwamoto *et al*, SBT 2004).

Immune Inactivation by Tumor-Derived Cytokines: IL-10

- Expression of IL-10 in gastric carcinoma as determined by immunohistochemistry correlates with LN metastases and reduced 5 yr survival (Sakamoto *et al*, SBT 2004).

Immune Inactivation by Tumor-Derived Cytokines: MIF

- MIF produced by neuroblastomas blocks T cell activation through the TCR and induces apoptosis in activated T cells, possibly through IFN-γ induction (Orentas *et al*, SBT 2004).

T Cell Inactivation by TAMs

- Production of IL-10
- Production of CCL18 (Mantovani *et al*, SBT 2003)
- Production of O_2 radicals, which can kill tumoricidal lymphocytes via a caspase-independent mechanism involving PARP (Thorén *et al*, SBT 2004).

Tumor Cell Expression of Ligands for Negative Regulatory Receptors on T Cells

- Fas-L
- PD-L1 (B7H-1) on melanoma cells (Gajewski *et al*, Cancer Res 2004).
- Shed MICA down regulates NKG2D on T cells and reduces the response of tumor antigen-specific T cells to tumor cells (Groh *et al*, SBT 2003).

Tumor Cell Expression of Ligands for Negative Regulatory Receptors on T Cells

- Receptor-binding Cancer Antigen on SiSo (uterine adenocarcinoma) cells (RCAS-1) induces apoptosis in T and NK cells expressing the receptor. Expression correlates with LN metastasis, reduced TIL, TIL apoptosis, and poor prognosis in patients with GI tract tumors (Tsujitami *et al*, SBT 2004).

Tumor Cell Expression of Ligands for Negative Regulatory Receptors on T Cells

- CD200 (on CLL) blocks IFN-γ production by cocultures of human macrophages and T cells (Kretz-Rommel, SBT 2004).

CONCLUSIONS

- Tumors are selected *in vivo* for their ability to evade immune recognition and effector cell function.
- Established tumors may utilize any of several mechanisms to evade surveillance.
- Vaccination and other forms of immunotherapy will have limited clinical benefit until the mechanisms by which tumor cells insulate themselves from the immune system are identified and methods developed to thwart these processes.