PD-L1 Expression and Signaling by Tumors and Macrophages: Comparative Studies in Mice and Dogs

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PD-1 and PD-L1 checkpoint pathways targeted by antibody therapeutics
Major points to cover

• PD-L1 expression and regulation on canine tumor cells and macrophages: Heterogeneity and cytokine regulation
• Differential regulation of PD-L1 expression on tumor cells vs tumor-associated macrophages: Role of TNF pathway
• Negative regulation of macrophage function by PD-L1: Interruption of constitutive signaling by PD-L1 mAbs
• Opportunities for collaboration in canine immuno-oncology
Canine tumor cells all express PD-L1 in vitro

(Gen Hartley)
IFN-γ upregulation of canine tumor PD-L1 expression

(Hartley G, et al, VCO, 2016)
Cytokine regulation of macrophage PD-L1 expression in dogs

Tumor macs express PD-L1

T cell infiltrates and PD-L1 association

CD11b

PD-L1

CD3

PD-L1
Tumor tissues express variable amounts of PD-L1
How is PD-L1 expression regulated on tumor macrophages in vivo?

PD-L1 expression by tumor cells

PD-L1 expression by tumor macrophages

Tumors secrete a factor that upregulates monocyte PD-L1 expression

Tumor secreted factors

Cytokines
Tumor macrophages are the major cells expressing PD-L1 and producing TNF-α.
Tumor matrix proteoglycans upregulate monocyte PD-L1 expression by stimulating macrophage TNF-a production
Does PD-L1 signal to tumor infiltrating macrophages?
Signaling by PD-1 and PD-L1: Immunological effects
Canine PD-1 blockade reverses T cell suppression by tumors

(PD-1 mAb + tumor cell line)

(Tumor explant cultures)

(Coy J, et al, VCO, 2017)
What happens when macrophages are incubated with PD-L1 Abs?
PD-L1 Ab induces macrophage size, proliferation, and survival
PD-L1 antibody also induces macrophage activation
PD-L1 blockade by sPD-1 also activates macrophages, but less potent
PD-L1 delivers constitutive inhibitory signal to macrophages
PD-L1 Ab treatment in vivo increases macrophage numbers and activation in tumors
Tumor growth inhibition in TNFR-/- mice: Does decreased PD-L1 expression by tumor macrophages explain this effect?
Implications for treatment with PD-L1 and PD-1 antibodies

1. PD-L1 Ab treatment not equivalent to PD-1 treatment
2. PD-L1 blockade activates tumor infiltrating macrophages, PD-1 blockade does not
3. Dual administration of PD-1 and PD-L1 Abs likely to be additive or synergistic
Current immune-oncology studies in dogs at ACC: Opportunities for collaboration

- New therapeutics for modifying the TME: monocyte migration inhibitors and innate immune activators
- Tumor vaccines targeting cancer stem cells
- Identification of tumor neoantigens in lymphoma
- Checkpoint molecule antibody development
- New immune reagents: exhausted T cells, myeloid cells
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