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The aryl hydrocarbon receptor in tumor immunity

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The aryl hydrocarbon receptor (AHR) binds environmental toxins and mediates immune regulation. The tryptophan metabolite kynurenine has now been identified as an endogenous ligand of the human AHR constitutively produced by gliomas and other types of cancer via tryptophan-2,3-dioxygenase (TDO), thereby suppressing antitumor immune responses via the AHR. Thus, this pathway represents an important novel target for cancer immunotherapy.

The aryl hydrocarbon receptor (AHR) is a basic helix-loop-helix (bHLH) Per-Arnt-Sim (PAS) family transcription factor, which is expressed in a variety of cells and activated by xenobiotics such as benzo [*a*]pyrene and 2,3,7,8-tetrachlordibenzo-dioxin (TCDD).[1] There is increasing evidence that the AHR reaches far beyond simply binding xenobiotics to induce a metabolic machinery (cytochrome P450 oxidases) that eliminates these toxic compounds from the body. The largest body of evidence for additional functions of the AHR, particularly regulating immune responses, stem from in vivo studies with TCDD, which binds and activates the AHR but resists metabolic degradation. For instance, treatment of mice with autoimmune neuroinflammation with TCDD suppresses encephalitogenic T cell responses and ameliorates disease severity.[2] The AHR is enriched in interleukin 17 (IL-17)-producing CD4+ T cells (T_H17 cells) and controls the differentiation of naïve CD4+ T cells.[2,3] Its function in the context of T helper cell differentiation appears to be conferred by ligand-dependent signal strength and duration and thus result in the generation of regulatory T cells (T_{reg}) or T_H17.[2,3] In addition, AHR influences dendritic cell (DC) function.[4] Whether the AHR is expressed in and influences the function of CD8+ T cells is still a matter of debate, which may be a reason why the role of the AHR has not been explored in the context of tumor immunity thus far. Another reason may reside in the uncertainty of an endogenous ligand activating the AHR in the tumor micromilieu. Endogenously produced compounds such as arachidonic acid metabolites, bilirubin, cAMP, as well as tryptophan catabolites such as tryptamine and 6-formylindolo [3,2-b]carbazole (FICZ) are ligands of the promiscuous AHR with potential relevance both in physiological conditions and cancer. In addition the immediate tryptophan (Trp) metabolite kynurenine (Kyn), which is known to suppress antigen-specific T-cell responses,[5] has been shown to promote T_{reg} differentiation via the AHR.[6] However, whether these endogenous AHR ligands are produced in the tissue microenvironment in amounts sufficient to modulate immune responses had not been shown to date. We have shown that malignant glioma produce enough Kyn from Trp to activate the AHR due to a high constitutive activity of the tryptophan-2,3-dioxygenase (TDO).[7] The fact that TDO is responsible for Trp metabolism in glioma was surprising as its expression was previously thought to be restricted to liver and neural cells and as Trp catabolism in tumors had been attributed to the enzymatic activity of indoleamine-2,3-dioxygenase 1 (IDO1). In fact, IDO1 is a key factor of the tumor microenvironment suppressing tumor immunity and promoting immune evasion.[8,9] Our study suggest that tumor-derived TDO is equally capable of inducing immunosuppression as TDO-expressing tumors resist immune-mediated lysis and as strong TDO-expression in human tumors is associated with fewer infiltrating CD8+ T cells.[7] Two observations suggest that the AHR is mediating immunosuppression by TDO: (A) Immune infiltration in TDO-expressing tumors is restored in AHR-deficient mice; and (B) AHR target genes such as the TCDD-inducible poly [ADP-ribose] polymerase (TIPARP), which has high homology to TIL, a gene isolated from tumor-infiltrating T cells,[10] are specifically induced in immune cells infiltrating TDO-positive but not TDO-negative tumors.[7] Kyn is not a low affinity AHR ligand. In radioligand assays the apparent K_d was around 4 μM, the EC_{50} was 12.3 μM in enzymatic assays and 36.6 μM in reporter assays. Since the mean tissue concentration in TDO-expressing tumors was 37 μM and since concentrations of up to 60 μM were measured in the cell culture supernatant of TDO-expressing tumors Kyn-production in gliomas is within a relevant range to activate the AHR.[7] There are three central questions that need to be addressed: (1) Is the AHR the sole mediator of immunosuppressive Trp catabolism in the tumor microenvironment, (2) what are the cellular determinants of AHR-mediated

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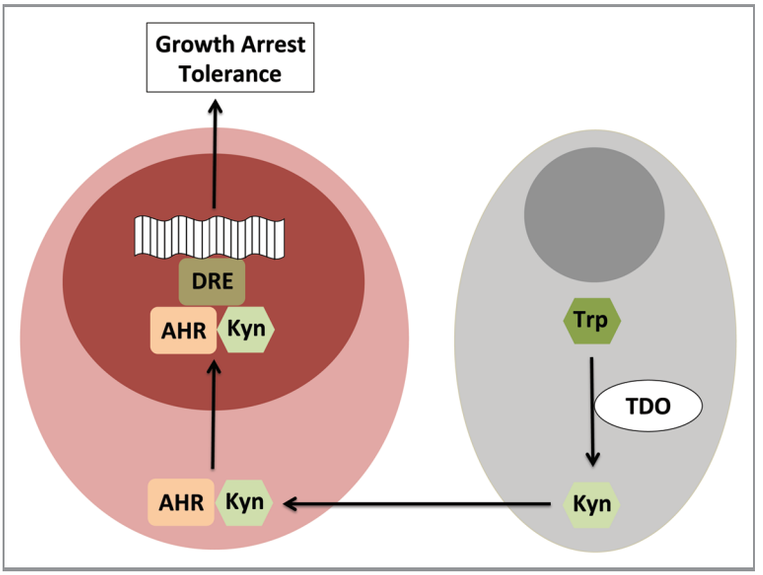

Figure 1. Tumor cells (gray) with active tryptophan-2,3-dioxygenase (TDO) convert tryptophan (Trp) to kynurenine (Kyn), which is secreted in the extracellular space and binds the aryl hydrocarbon receptor (AHR) in neighboring immune cells (red), where it induces its translocation into the nucleus. The AHR binds dioxin responsive elements (DRE) in the promoter of its target genes, suppressing proliferation and function of immune cells thus suppressing tumor immune responses.

suppression of tumor immune responses and (3) what are the molecular targets? As direct experimental evidence is currently lacking one can only speculate on the answers: 1) Depletion of Trp from the micromilieu may be sufficient to induce immunosuppression by activating the integrated stress response in T cells. Possibly, the net effect is a combination of both, depletion of Trp and accumulation of Kyn. 2) Kyn may act on the AHR on T cells and dendritic cell, two key components of tumor immunity.[4,6] Based on the observations in autoimmune disease models it is tempting to speculate that TDO-derived Kyn induces T_{reg} cells that in turn suppress tumor-specific CD8+ T cells. It may, however, be equally possible that Kyn acts directly on tumor-specific CD8+ T cells or via generating tolerogenic DC in an AHR-dependent fashion. These questions can only be answered using conditional knockout mice that are already available. 3) While TIPARP may be an intriguing candidate target gene of the AHR in T cells, we found broad induction of AHR-dependent genes by Kyn that are related to immune responses for instance interleukin-1beta (IL-1b), IL-6 or chemokines such as CCL2. The contribution of these AHR target genes in the context of tumor immunity will have to be determined. What's clear from our data is that the AHR represents a novel therapeutic target in glioma and possibly other types of cancer to revert local immunosuppression in the tumor microenvironment possibly as an adjunct to active immunotherapies.

References

1. Denison MS, Nagy SR. Activation of the aryl hydrocarbon receptor by structurally diverse exogenous and endogenous chemicals. Annu Rev Pharmacol Toxicol 2003; 43:309-34; PMID:12540743; http://dx.doi.org/10.1146/annurev.pharmtox.43.100901.135828
2. Quintana FJ, Basso AS, Iglesias AH, Korn T, Farez MF, Bettelli E, et al. Control of T(reg) and T(H)17 cell differentiation by the aryl hydrocarbon receptor. Nature 2008; 453:65-71; PMID:18362915; http://dx.doi.org/10.1038/nature06880
3. Veldhoen M, Hirota K, Westendorf AM, Buer J, Dumoutier L, Renauld JC, et al. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. Nature 2008; 453:106-9; PMID:18362914; http://dx.doi.org/10.1038/nature06881
4. Quintana FJ, Murugaiyan G, Farez MF, Mitsdoerffer M, Tukpah AM, Burns EJ, et al. An endogenous aryl hydrocarbon receptor ligand acts on dendritic cells and T cells to suppress experimental autoimmune encephalomyelitis. Proc Natl Acad Sci USA 2010; 107:20768-73; PMID:21068375; http://dx.doi.org/10.1073/pnas.1009201107
5. Platten M, Ho PP, Youssef S, Fontoura P, Garren H, Hur EM, et al. Treatment of autoimmune neuroinflammation with a synthetic tryptophan metabolite. Science 2005; 310:850-5; PMID:16272121; http://dx.doi.org/10.1126/science.1117634
6. Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, Bradfield CA. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. J Immunol 2010; 185:3190-8; PMID:20720200; http://dx.doi.org/10.4049/jimmunol.0903670
7. Opitz CA, Litzenburger UM, Sahm F, Ott M, Tritschler I, Trump S, et al. An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. Nature 2011; 478:197-203; PMID:21976023; http://dx.doi.org/10.1038/nature10491
8. Muller AJ, DuHadaway JB, Donover PS, Sutanto-Ward E, Prendergast GC. Inhibition of indoleamine 2,3-dioxygenase, an immunoregulatory target of the cancer suppression gene Bin1, potentiates cancer chemotherapy. Nat Med 2005; 11:312-9; PMID:15711557; http://dx.doi.org/10.1038/nm1196
9. Uyttenhove C, Pilotte L, Theate I, Stroobant V, Colau D, Parmentier N, et al. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. Nat Med 2003; 9:1269-74; PMID:14502282; http://dx.doi.org/10.1038/nm934
10. Ma Q, Baldwin KT, Renzelli AJ, McDaniel A, Dong L. TCDD-inducible poly(ADP-ribose) polymerase: a novel response to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Biochem Biophys Res Commun 2001; 289:499-506; PMID:11716501; http://dx.doi.org/10.1006/bbrc.2001.5987