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METABOLISM

Catabolic effects

The enzymes indoleamine 2,3-dioxygenase 1 (IDO1), IDO2 and tryptophan 2,3-dioxygenase (TDO) mediate the breakdown of Trp to kynurenine (Kyn). IDO proteins inhibit antitumour immune responses and IDO inhibitors are being tested in patients with cancer, but the mechanisms by which Trp catabolism promotes tumorigenesis, and the contributions of TDO, are unknown.

Opitz *et al.* found high levels of Kyn secreted from human glioma cell lines; this was inhibited by short hairpin RNA-mediated knockdown of TDO but not IDO proteins. In addition, increased TDO expression correlated with increasing malignancy of human glioma samples. How does Kyn promote tumorigenesis? Kyn is known to suppress T cell proliferation; the authors confirmed this paracrine effect by culturing T cells with glioma cells. Furthermore, human gliomas expressing high levels of TDO had lower $CD8^+$ T cell and leukocyte infiltration than those that expressed low levels of TDO. In mice, subcutaneous tumours from *Tdo*-null mouse glioma cells engineered to overexpress TDO grew faster than parental cells, and antitumour immune responses were suppressed. Kyn also had autocrine effects: TDO knockdown or Trp withdrawal in glioma cells decreased cell motility and clonogenic survival. Tumour growth in the brains of nude mice (which lack functional T cells) was also inhibited by TDO knockdown, suggesting that autocrine effects of Kyn have a role in tumorigenesis.

To further understand the autocrine effects of Kyn, the authors conducted microarray analyses of glioma cells and found that genes transcribed by aryl hydrocarbon receptor (AHR) were induced. Exogenous toxins activate this transcription factor (which has previously been implicated in tumorigenesis), but the authors demonstrated that endogenous Kyn in glioma cells could also activate AHR. Infiltration of immune cells into TDO-expressing tumours was attenuated in *Ahr*-proficient, but not $Ahr^{-/-}$ host mice, underscoring the importance of AHR in suppressing immune cell recruitment. Interestingly, TDO-expressing tumours were larger than TDO-deficient tumours in $Ahr^{-/-}$ mice, and AHR knockdown reduced Kyn-mediated motility and survival of glioma cells, supporting the hypothesis that Kyn has autocrine effects on tumour cells expressing AHR.

Does this pathway function in human tumours? Expression of *TDO* and the encoded protein correlated with expression of *AHR*, AHR target genes and the respective encoded proteins in human glioma tissue; similar results were found using microarray data from several other tumour types. In addition, analyses of microarray data showed that patients with gliomas that highly expressed *TDO*, *AHR* or AHR target genes had reduced overall survival compared with patients whose tumours expressed lower levels of these genes.

In addition to showing that TDO and IDO proteins have similar functions in tumours, this paper has linked Trp catabolism to AHR activation as a mechanism to enhance tumour cell motility, survival and immune evasion.

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> “patients with gliomas that highly expressed *TDO*, *AHR* or AHR target genes had reduced overall survival”

ORIGINAL RESEARCH PAPER Opitz, C. A. *et al.* An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. *Nature* 5 Oct 2011 (doi:10.1038/nature10491)
FURTHER READING Löb, S. *et al.* Inhibitors of indoleamine-2,3-dioxygenase for cancer therapy: can we see the wood for the trees? *Nature Rev. Cancer* **9**, 445–452 (2009)