Regulation of prostaglandin synthesis and cell adhesion by a tryptophan catabolizing enzyme

ABSTRACT

These results suggest that catabolism of the rarest essential amino acid may regulate processes such as cell adhesion and prostaglandin synthesis.

INTRODUCTION

Background Two known enzymes catabolize the essential amino acid tryptophan in mammals. Tryptophan 2, 3 dioxygenase (TDO) is expressed predominantly in hepatic tissues and was the first inducible enzyme system discovered in mammals. It controls serum tryptophan homeostasis and is induced following ingestion of tryptophan. A second enzyme, IDO, is distinguished from TDO by its expression pattern, substrate specificity and inducibility. IDO is expressed in a variety of non-hepatic tissues, including placenta, lung, gut and epididymis. Except for the last named tissue where IDO is expressed constitutively, IDO is inducible by inflammatory mediators, including interferons. In addition, IDO catalyzes the breakdown of a variety of compounds which contain an indole ring, including D-tryptophan and serotonin, marking another difference from TDO, which is specific for L-tryptophan. Curiously, it appears as if tryptophan itself cannot induce IDO synthesis. IDO is also suggested to be the evolutionary ancestor of certain novel myoglobins which occur in molluscs, marking IDO as an evolutionarily primitive enzyme. IDO is known to be expressed in cells infected with intracellular pathogens such as Toxoplasma and Chlamydia species and also by viruses. In the case of Toxoplasma and Chlamydia it has been proposed that IDO induction is a cellular defense mechanism, designed to limit the proliferation of the invading pathogen by depleting the essential amino acid tryptophan. IDO expressed in monocyte derived macrophages has also been found to inhibit the growth of extracellular bacteria such as group B streptococci, and is also induced in tumors taken from cancer patients. In all of these systems the proximal inducer of IDO activity is interferon-γ (IFN-γ). Response elements for this cytokine have been identified in the human IDO promoter and have been shown to be essential for IFN-γ induction of reporter gene expression in vitro. The unusual tissue distribution of IDO suggests that combating infection is not its only function. Our interest in IDO arose when we observed that tryptophan depletion was responsible for macrophage-induced inhibition of T cell proliferation in vitro. Furthermore, we reported that a pharmacologic inhibitor of IDO, 1-methyl tryptophan, induced maternal rejection of allogeneic but not syngeneic murine fetuses. As IDO is strongly expressed at the maternal-fetal interface in pregnant mice and women, we have suggested that IDO plays a role in fetal defense against the maternal immune system and could represent a novel means of immunoregulation. The apparently diverse functions and tissue distribution of IDO may have as a common theme the fact that tryptophan is the rarest essential amino acid and could be the target for cellular regulatory mechanisms. If so, tryptophan concentrations in cellular microenvironments might play a critical role in modulating various cellular processes in a way that cannot be achieved by the hepatic enzyme TDO which regulates systemic tryptophan concentrations. The IDO promoter contains a diverse collection of motifs together with the IFN-γ response elements. These include motifs for transcription factors that bind to collagenase and elastase genes and motifs for the transcription factor MEP-1, which regulates transcription from the stromelysin-1 (MMP-3) and

metallothionein genes. Matrix metalloproteinases (MMPs) are responsible for modification of the extracellular matrix and are involved in wound healing, tumorigenesis, pregnancy and inflammation. In general, they regulate how cells interact with each other and with the extra-cellular matrix. Evidence for a tryptophan-reversible inhibition of MMP expression by IFN-γ has previously been presented, although the exact mechanism is unclear. Therefore we decided to directly test whether IDO plays a role in controlling interactions with other cells and also the surrounding extracellular environment. We have identified cells expressing IDO in vitro and used IDO antisense constructs to inhibit this expression. In addition, we have constitutively overexpressed IDO in adherent and non-adherent cell lines in vitro. Our results demonstrate that tryptophan catabolism has significant effects on cell adhesion and regulates the activity and expression of cyclooxygenases 1 and 2 (COX-1 and -2).

CONCLUSION

Conclusions IDO regulates adhesion of cells to normal growth substrates. In so doing it modulates the expression and activity of COX-2 and certain MMPs. RAW cells and MC57 cells overexpressing IDO grew as multicellular foci. In the case of RAW cells, this was due to elevated PGE relative to other prostaglandins. P19 cells in which endogenousIDO expression was disrupted by antisense expression, showed lower adhesiveness. Thus, tryptophan catabolism exerts control over fundamental cellular functions.