INVOLVEMENT OF THE AH RECEPTOR IN ALTERATIONS IN IMMUNE SYSTEM DEVELOPMENT

Jacqueline McGuire[1], Patrik Andersson[1,2], Anna Ridderstad Wollberg[3], Annika Hanberg[2] and Lorenz Poellinger[1]

[1] Department of Cell and Molecular Biology, Medical Nobel Institute, Karolinska Institute, S-171 77 Stockholm, Sweden.
[2] Institute of Environmental Medicine, Karolinska Institute, S-171 77 Stockholm, Sweden.
[3] Astra AB, 151 85 Södertälje, Sweden.

Introduction

The intracellular, bHLH/PAS dioxin [aryl hydrocarbon, Ah] receptor (AhR) is a ligand – activated transcription factor that mediates the adaptive and toxic responses to environmental pollutants such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and structurally related congeners[1-5]. In the absence of ligand, the receptor is recovered as a latent, non-DNA binding heteromeric complex with the molecular chaperone hsp90. Exposure to ligand initiates a multi-step activation process which results in the release of hsp90 and dimerization with the structurally related partner factor Arnt. The AhR-Arnt heterodimer then binds to specific enhancer elements upstream of target promoters and activates genes involved the metabolism of xenobiotics such as CYP1A1[2-5].

In addition to the induction of drug metabolising enzymes, the AhR is believed to mediate the plethora of toxic responses observed in all species studied to date resulting from exposure to TCDD. These include immune suppression, thymic involution, endocrine disruption, a lethal wasting syndrome, teratogenesis, epithelial hyperplasia, tumor promotion and carcinogenesis[1-5]. In contrast to the induction of xenobiotic metabolism however, relatively little is known regarding the molecular basis by which the receptor mediates these toxic endpoints.

Results and Discussion.

We have recently defined a mutant of the AhR that functions as a potent constitutive activator of transcription (CA – AhR). We envisaged that such a mutant should mimic the toxicological effects that are normally attributed to the TCDD - activated form of the receptor. In addition, such a mutant could potentially provide insights into the putative physiological role of the receptor.

Since the immune system has been identified as a particularly sensitive target for the toxic effects associated with exposure to TCDD[6,7], we created transgenic mice ectopically expressing the dominant positive AhR mutant coupled to the immunoglobulin heavy chain enhancer (Eμ) which has previously been shown to promote transgene expression in both the B and T cell lineages[8,9]. Mice homozygous for the CA – AhR transgene are both viable and fertile. Relative thymus weights in these animals were found to be decreased as compared to wild type animals up to the age of six months. An increased population of single positive $CD8^+$ and a decreased population of $CD4^+$ T cells was observed in the thymus of new born CA – AhR mice. This effect however, could not be detected in adult mice. Analysis of B cell populations within the bone marrow, revealed significant increases in the pro-B cell, pre-B cell, virgin B cell and mature B cell compartments. Furthermore, analysis of the B cell compartment of the peritoneum demonstrated a dramatic reduction in the $CD5^+$ B1 cell population.

References

1. Poland A. and Knutson J. (1982) Annu. Rev. Pharmacol. Toxicol. 22, 517.
2. Hankinson O. (1995) Somatic Cell Genet. 9, 497.
3. Poellinger L. (1995) In: Inducible Gene Expression Vol. 1, Ed.: P. A. Baeuerle, Birkhäuser, Boston, USA.
4. Okey A. B., Riddick D. S. and Harper P. A. (1994) Trends Pharmacol. Sci. 15, 226.
5. Schmidt J. V. and Bradfield C. A. (1996) Annu. Rev. Cell Dev. Biol. 12, 55.
6. Holsapple M. P., Morris D. M., Wood S. C. and Snyder N. K. (1991) Annu. Rev. Pharmacol. Toxicol. 31, 73.
7. Kerkvliet, N.I. (1995). Environ.Health Perspect. 103 (Suppl:9):47.
8. Adams J. M. and Cory S. (1991) Science 254, 1161.
9. Bodrug S. E., Warner B. J., Bath M. L., Lindeman G. J., Harris A. W. and Adams J. M. (1994) EMBO 13, 2124.