Molecular and Cellular Endocrinology 457 (2017) 81–88

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Acromegaly, genetic variants of the aryl hydrocarbon receptor pathway and environmental burden

S. Cannavo, F. Trimarchi, F. Ferraù*

Department of Clinical and Experimental Medicine - Endocrinology Unit, University of Messina, Italy

ARTICLE INFO

Article history:
Received 17 September 2016
Received in revised form
15 December 2016
Accepted 16 December 2016
Available online 18 December 2016

Keywords:
Acromegaly
AHR
AIP
Pollution
Endocrine disruptors

ABSTRACT

Increasing evidence suggests that environmental contaminants can exert endocrine disruptors activities and that pollution exposition can have a role in tumorigenic processes. Several environmental pollutants have been shown to affect pituitary cells biology and function. The aryl hydrocarbon receptor (AHR) pathway is involved in xenobiotics' metabolism and in tumorigenesis. A deregulation of the AHR pathway could have a role in pituitary tumours' pathophysiology, especially in the GH secreting ones. AHR-interacting protein (AIP) is one of the key partners of AHR and is implicated in pituitary tumours' pathogenesis. Moreover, an increased prevalence of acromegaly has been reported in a highly polluted area of the province of Messina (Sicily, Italy). Nevertheless, at present, few data are available about the potential role of environmental factors in the pathogenesis and clinical expression of GH secreting pituitary tumours. This review is aimed at discussing the evidences on the potential links among environmental pollutants, the AHR pathway and the pathophysiology of GH-secreting pituitary adenomas.

1. Introduction

Acromegaly is a rare disease characterised by an abnormal growth of bone, soft tissues and organs, as a consequence of a growth hormone (GH) excess due – in most of the cases – to a pituitary adenoma (Broder et al., 2016; Capatina and Wass, 2015; Dal et al., 2016; Daly et al., 2006; Melmed, 2009; Mestron et al., 2004). The estimated prevalence of acromegaly has been variably reported between 34 and 125 cases per million of persons (cpm), although it has been shown to be even higher in some studies (Cannavo et al., 2010). Acromegaly is generally diagnosed after several years from disease onset with considerable clinical, economical and social consequences (Capatina and Wass, 2015). To date, the pathogenic mechanisms underlying the development, progression and clinical impact of GH-secreting pituitary tumours are only partially disclosed.

Some studies have shown that environmental pollutants with endocrine disruptors activities can impact on pituitary function and biology (Gore, 2010). It's known that the aryl hydrocarbon receptor (AHR) is the main actor of the intracellular mechanisms of xenobiotics' metabolism and detoxification, and can influence the major stages of tumorigenesis (Fig. 1) (Dietrich and Kaina, 2010; Feng et al., 2013; Hao and Whitelaw, 2013). However, data on the role of environmental pollutants and of the alterations of the AHR pathway in pituitary tumorigenesis are scanty. On the other hand, the AHR cytosolic stabilization, function and signalling pathway are strictly dependent on the AHR-interacting protein (AIP) that in turn has a key role in pituitary tumour development (Beckers et al., 2013; Beischlag et al., 2008; Hao and Whitelaw, 2013; Petrulis and Perdew, 2002; Trivellin and Korbonits, 2011). Indeed, AIP gene mutations have been found in about 20% of patients with familial isolated pituitary adenoma syndrome (FIPA) and in 40% of patients with isolated familial somatotropinomas, as well as in up to 4% of patients with apparently sporadic acromegaly (Beckers et al., 2013; Ferrau et al., 2016; Hernandez-Ramirez et al., 2015; Lloyd and Grossman, 2014). Pituitary tumours associated with AIP gene mutations are mainly GH and/or PRL secreting, show an aggressive clinical and biochemical phenotype, occur more frequently in young patients and are more resistant to conventional treatments (Alband and Korbonits, 2014; Beckers et al., 2013; Martucci et al., 2012). In this review, the evidence on the potential links among environmental pollutants, the AHR pathway and the pathophysiology of GH-secreting pituitary adenomas will be discussed.

* Corresponding author. UOC di Endocrinologia, Pad. H, 4 piano, AOU Policlinico Gaetano Martino, Via Consolare Valeria, 1, 98125, Messina, Italy.
E-mail address: francesco.ferrau1@gmail.com (F. Ferraù).

http://dx.doi.org/10.1016/j.mce.2016.12.019
0303-7207/

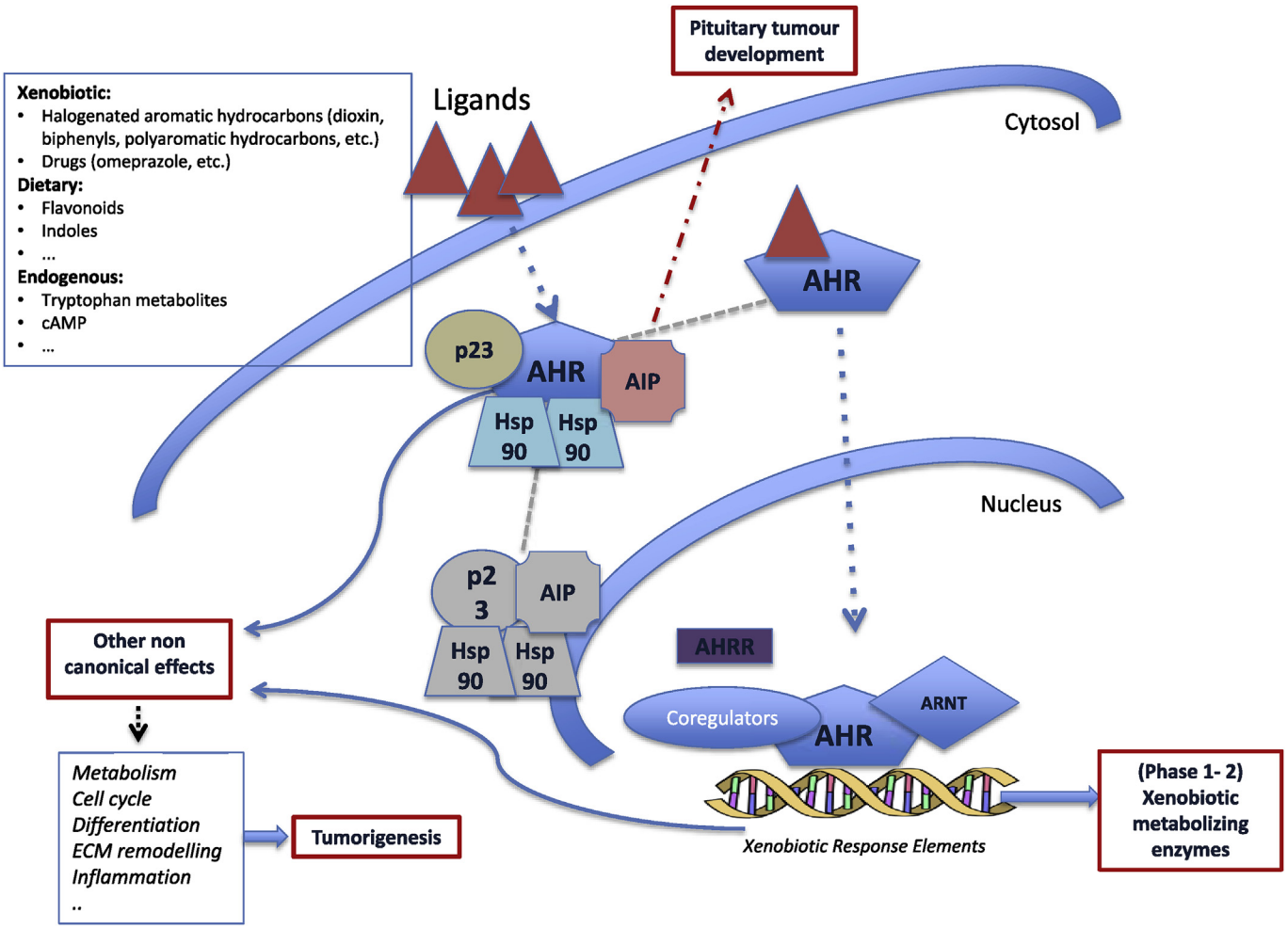

Fig. 1. In the cytosol, the unbound aryl hydrocarbon receptor (AHR) forms a complex with AHR-interacting protein (AIP), the co-chaperone protein p23 and two heat shock protein 90 (Hsp90) molecules. AIP is an oncosuppressor involved in the pathogenesis of pituitary tumours. AHR recognises several exogenous and endogenous ligands, whose binding results in nuclear translocation of AHR, dissociation from the chaperone proteins, heterodimerization with a nuclear translocator (ARNT) and subsequent binding to xenobiotic-responsive elements (XREs) modulated by other coregulators. This leads to transactivation of several genes encoding phase I and II xenobiotic metabolizing enzymes, such as cytochrome P450s (CYP1A1, CYP1A2 and CYP1B1), as well as other genes coding for non-enzymatic proteins. Other genomic and non-genomic 'non-canonical' effects (on the cell-cycle, contact inhibition, cell adhesion, function and metabolism of the oestrogen receptors, and DNA repairing processes) can be the direct consequence of the activation of this transcriptional factor, contributing to the disruption of cell homeostasis and tumorigenic processes. AHRR: AHR repressor.

2. The AHR-AIP pathway

The AHR is a transcription factor belonging to the basic helix-loop-helix/Per/ARNT/Sim (PAS) family (Dietrich and Kaina, 2010). It is stimulated by several natural compounds which are present in food, as indoles and flavonoids, or by tryptophan derivatives, arachidonic acid metabolites and other endogenous products (Denison and Nagy, 2003; Denison et al., 2002; Dietrich and Kaina, 2010). The most potent AHR ligand known so far is the 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) but more than 400 exogenous compounds act as AHR ligands, most of which are environmental endocrine disruptors, including a variety of polycyclic aromatic hydrocarbons and planar polychlorinated biphenyls (PCBs) (Denison and Nagy, 2003; Denison et al., 2002; Dietrich and Kaina, 2010).

It is generally accepted that the metabolic responses to environmental pollutants can be the direct consequence of AHR activation. In the cytosol, the unbound receptor forms a complex with AIP, the co-chaperone protein p23 and two heat shock protein 90 (Hsp90) molecules. Ligand binding results in nuclear translocation of AHR, dissociation from the chaperone proteins, heterodimerization with a nuclear translocator (ARNT) and subsequent binding to xenobiotic-responsive elements (XREs) (Fig. 1). This leads to transactivation of several genes encoding phase I and II xenobiotic metabolizing enzymes, such as cytochrome P450s (CYP1A1, CYP1A2 and CYP1B1), as well as other genes coding for non-enzymatic molecules or proteins like the cyclin-dipendent kinases inhibitor p27Kip1 (Denison and Nagy, 2003; Dietrich and Kaina, 2010; Feng et al., 2013; Hao and Whitelaw, 2013). The functional relevance of the AHR pathway is not restricted to the cellular response to the toxic insult, since others 'non-canonical' effects (on the cell-cycle, contact inhibition, cell adhesion, function and metabolism of the oestrogen receptors, and DNA repairing processes) can be the direct consequence of the activation of this transcriptional factor, further contributing to the disruption of cell homeostasis (Denison and Nagy, 2003; Dietrich and Kaina, 2010; Feng et al., 2013).

The AHR plays a relevant role in tissue-specific embryonic development, hematopoietic stem cell self-renewal, pluripotent stem cell and neural stem cell differentiation, and erythroid stem cell growth, as well as in development of cells with cancer stem cell-like qualities (Gasiewicz et al., 2014; Mulero-Navarro and