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Title: Cell migration and metastasis markers as targets of environmental pollutants and the Aryl hydrocarbon Receptor

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Abstract

During the last few years, several studies have pointed to a surprising link between environmental pollutants cellular signaling and important cell functions such as plasticity, adhesion and migration. This unexpected link could be related to endogenous functions of pollutants receptors that may be disrupted by environmental factors, which is supported by observations in invertebrate species. It could also reveal novel toxic endpoints and mechanisms of those pollutants, such as teratogenesis and cancer metastasis that are highly relevant from a public health point of view. In the present short article, we will review our recent observations on the aryl hydrocarbon receptor and its new molecular and cellular targets. We identified HEF1/NEDD9/CAS-L, a multifunctional protein involved in integrin-based signaling as a transcriptional target of the receptor, and showed that its induction was critical for cell plasticity mediated by environmental pollutants. We will put our studies in perspective with other observations made by several groups.

Populations of industrialized and third world countries are commonly exposed to numerous organic contaminants or pollutants. Several of them are persistent in the environment and accumulate in the adipose tissue of animals and humans ¹; those Persistent Organic Pollutants (POP) are characterized by a long half-life and are slowly metabolized. They are known to elicit a variety of toxic effects that are related to their molecular structure and their mechanism of action ². The influence of some pollutants on tumor initiation and promotion has been clearly demonstrated (ex: benzo(a)pyrene in tobacco smoke). Remarkably, few studies have been undertaken to establish a relationship between exposure to POPs and tumor progression, particularly metastasis development, which is responsible of 90% cancer deaths and poor end-of-life conditions (www.iarc.fr). While some environmental risk factors have been clearly identified as critical tumor initiators and promoters (UV, tobacco,), little is known on the possible role of those factors on tumor progression and metastasis. Obviously, such findings would be highly relevant for public health and would improve our knowledge on the relationship between environment and cancer.

The AhR, a xenobiotic receptor

Several POPs as well as other pollutants bind and activate an intracellular receptor called the Aryl hydrocarbon Receptor (AhR). We have recently identified the AhR as a regulator of cellular processes reminiscent of epithelial-mesenchymal transition (EMT), a phenomenon, which has been linked to tumor metastasis ³. The AhR is a member of the bHLH/PAS (basic Helix Loop Helix/Per ARNT Sim) family ⁴, which has been identified as a receptor of environmental pollutants including polyaromatic aromatic hydrocarbons (PAH), polyhalogenated hydrocarbons like dioxins, furans and polychlorinated biphenyls (PCBs) and polyphenols. This wide ligand spectrum is abundantly represented in our

ecosystems (cigarette smoke, combustion products, contaminated food (dioxins, PAH, PCBs...), natural food products (polyphenols, metabolites derivatives...)) and as a consequence, human populations are daily exposed to AhR ligands⁵. Upon ligand binding, the cytosolic receptor behaves like a classical nuclear receptor and translocates into the nucleus, heterodimerizes with a partner named ARNT (AhR Nuclear Translocator) belonging to the same family (PAS) and binds to Xenobiotic Responsive Elements (or XRE) located in the promoters of target genes⁶. Historically, xenobiotic metabolizing enzymes have been identified as primary AhR targets; this pathway functions as an adaptive system allowing the sensing of xenobiotics, induction of their metabolism and transport and leading to their elimination^{7,8}. This auto regulatory loop is clearly critical for the cell and organism interactions with their environment. It should be noted that, considering this loop and compared to most classical AhR ligands, dioxins are particular because in fact, they are not metabolized by xenobiotic metabolizing enzymes. This could partly explain their long elimination half-life.

Regulation of HEF1 expression by the AhR

Knockout mouse AhR models have rapidly suggested that the AhR protein might have endogenous and alternative functions and this has been recently supported by studies in invertebrates models (fly, nematode) in which the AhR functions as a transcription factor but does not bind dioxin⁹⁻¹⁷. Transcriptomics experiments in mammalian model systems including ours, have allowed the identification of new gene targets of dioxin and the AhR; among them, we identified several putative regulators of migration¹⁸. Besides, we were able to show in the MCF-7 & HepG2 cell lines, that AhR activation (achieved by addition of ligands or using a cell line stably transfected with a constitutively activated AhR only expressed upon tetracycline withdrawal) leads to increased cell migration, Jun Kinases

activation and E-Cadherin downregulation¹⁸. These features (that we cautiously refer to as “cellular plasticity”) are reminiscent of EMT-related processes. EMT is defined as a phenotypic change (epithelial to mesenchymal) allowing the cell to migrate from its initial anchorage site to other niches; this is suspected to play a critical role in metastasis formation especially for epithelial cancers^{19,20}. In that initial study by Diry et al., we did not provide a mechanism to explain the effects of the AhR ligands. Recently, we and others implicated the metastasis marker HEF1/NEDD9/CAS-L as an essential node in AhR-regulated cell plasticity^{21,22}. HEF1/NEDD9/CAS-L is a multifunctional docking protein involved in integrin-based signaling that notably affects cell motility and oncogenic transformation^{23,24}. Moreover, it has been implicated in cilia stability and centrosome regulation^{25,26}. HEF1 interacts with focal adhesion kinase (FAK) and the Src family of tyrosine kinases, two critical regulators of focal adhesion²⁷. As a result, HEF1/NEDD9/CAS-L regulates migratory processes as demonstrated in a melanoma cell line²⁸; moreover, in several human cancers such as melanoma²⁸, glioblastoma²⁹ and lung tumors³⁰, increased HEF1/NEDD9/CAS-L expression was found to correlate with the metastasis potential of those tumors. On the other hand, other studies have also suggested a negative role for HEF1 in tumor progression^{31,32}. In our recent study, we show that several AhR ligands including dioxins and various common environmental pollutants (polycyclic aromatic pollutants) increase HEF1/NEDD9/CAS-L mRNA and protein expression in the hepatocarcinoma cell line HepG2; the mechanism is transcriptional and implicates AhR binding to HEF1/NEDD9/CAS-L promoter as stated by ChIP experiments. Moreover, when RNA interference was used to block HEF1 up regulation, the cellular plasticity phenotype elicited by dioxin, including JNK activation, E-Cadherin downregulation, focal adhesion sites remodeling and activation of cell migration, was inhibited

^{18, 22}. To our knowledge, this is the first observation revealing a link between common POPs exposure and increased expression of a metastatic marker.

The AhR is implicated in regulation of cell migration

The study supports the new concept that AhR is essential to regulate cell migration: indeed, using immortalized cell lines from wild-type (AhR+/+) and mutant (AhR-/-) mouse mammary fibroblasts, the team of Dr Pedro Fernandez-Salguero showed that AhR-deficient cells had a lower tendency to develop subcutaneous tumors in immunodeficient mice. In cell culture experiments, those cells also displayed reduced migration properties and lamellipodia formation. This could be related to the downregulation of the ERK-FAK-PKB/AKT-Rac-1 pathway in the AhR -/- cells ^{33, 34}. Interestingly, FAK activation status is also downregulated in mammary tumors arising in MMTV-polyoma virus middle T; Hef1 null mice ²⁴. In another recent study, the same team demonstrated the involvement of Vav3, a guanosine diphosphate/guanosine triphosphate exchange factor (GEF) for Rho/Rac GTPases (identified as a transcriptional target of AhR) in the regulation of those processes. AhR deficient immortalized and mouse embryonic fibroblasts have reduced expression of Vav3 and subsequent reduced Rac1 activity and increased activation of the RhoA/Rho kinase (Rock) pathway. Interestingly, Vav3 is sensitive to the AhR status (+/+ versus -/-) of the cell but not to xenobiotic exposure (dioxin). The consequences of this imbalance are an increased cell area, increased F-actin stress fibers, depolarized focal adhesions, and enhanced spreading and adhesion ³⁴. Interestingly, the AhR expression status does not lead to similar phenotypes in all cell models; indeed, the same team also showed that AhR deficiency increases keratinocyte migration and accelerates skin re-epithelialization probably because of a higher secretion of TGFbeta (transforming growth factor beta) by AhR null dermal fibroblasts ³⁵. The regulation of cell migration by the AhR

in the absence of xenobiotic exposure has also been observed in nematodes lacking the AhR ortholog, which display aberrant neuron migration, axon branching and axonal migration defects¹². While all of those experiments were performed using AhR-null models without stimulation by AhR ligands, other studies have reported an effect of dioxin or 3-methylcholanthrene (3MC, a polycyclic aromatic hydrocarbon) on cell migration: Peng et al and Seifert et al have reported increased gastric cancer cell invasiveness and MCF-7 cell migration upon TCDD addition and AhR activation^{36,37}. Moreover, Ikuta et al also observed the induction of a critical regulator of epithelial-mesenchymal transition (EMT), Slug, upon AhR nuclear translocation (upon 3MC stimulation or low cell density)³⁸. Again, this is not observed with all cell types as evidenced by a recent article showing that 3MC stimulation of HUVEC cells leads to reduced cell migration due to increased RhoA activity via suppression of a negative feedback pathway of FAK/p190RhoGAP³⁹.

Perspectives and conclusion

Several important points can be concluded from those studies: first, the regulation of cell migration by the AhR might be an ancestral function as clearly suggested by the invertebrates studies. Second, those articles and the ones reporting the use of AhR deficient cells, suggest that this process is not necessarily related to AhR stimulation by dioxins or aromatic hydrocarbons. Those studies do not rule out the possibility of AhR stimulation by endogenous ligands. Third, the involvement of the AhR in the regulation of migration appears to be clearly dependent on cell phenotypes (MEF, keratinocytes, cell lines). Interestingly, while we and others have suggested that AhR ligands might increase migration and invasion in various cell types, it is tempting to hypothesize that activation of the AhR during cancer promotion or progression reproduces developmental functions and might play a role in tumor progression. Finally, considering that HGF1 expression

varies considerably among tissues (mostly abundant *in vivo* in polarized cell populations) and cell cycle (abundant in G2/M) and that its levels are critical to ensure proper functions (centrosome regulation, integrin signaling) ⁴⁰, exposure to AhR ligands might disrupt those pathways ultimately leading to cancer or abnormal development. It should also be noted that the only *Drosophila* CAS family member (DCas) is highly expressed in the embryonic nervous system (such as the AhR ortholog) and that its expression is critical for axon guidance; indeed, DCas defect or overexpression lead to similar abnormal phenotypes ⁴¹. Moreover, a balanced HEF1 expression level is important for neuronal cell fate in mouse primary culture cells ⁴² or adhesion properties of chick neural crest cells ⁴³. Interestingly, those studies show that HEF1 expression is controlled by all-trans retinoic acid (atRA) and TGFbeta pathways ^{42,43}. Those connections between HEF1 expression and TGFbeta or atRA signaling have been also reported by other laboratories ⁴⁴⁻⁴⁷ and are particularly important regarding the AhR field. Indeed, the metabolism of atRA is clearly disrupted by expression of AhR-regulated cytochromes P450. Moreover, TGFbeta proteins regulate and are regulated by the AhR both *in vitro* and *in vivo* ⁴⁸.

The observations described above should be examined in light of the recent discoveries of common features between cancer and developmental pathways. While AhR knockout mice do not present a lethal phenotype at birth, they show several important developmental defects including liver fibrosis and cardiovascular abnormalities ^{9, 11}. Those studies as well as those performed with invertebrate models, suggest that the Aryl hydrocarbon receptor regulates developmental pathways such as cellular differentiation and migration in the absence of xenobiotic exposure. Interestingly, many of these pathways including cell migration, are critical for cancer growth and progression. We hypothesize that the disruption of AhR endogenous functions upon xenobiotic exposure might interfere with those pathways and ultimately lead, in a tumor cell, to the acquisition

of a mesenchymal/metastatic phenotype. The concept that part of pollutants toxicity stems from the disruption of essential endogenous functions of the AhR has rejuvenated the AhR field lately and will have to be further characterized in the future.

Legend of figure 1:

The AhR is a xenobiotic receptor, which forms a complex with chaperones in the cytoplasm. Upon ligand binding, it translocates to the nucleus and forms a transcription factor with its nuclear partner, ARNT. The heterodimer binds xenobiotic responsive elements (XRE) in the promoters of target genes. We identified HEF1/NEDD9/CAS-L as an AhR target. HEF1 induction is responsible for dioxin-mediated cell plasticity including E-Cadherin downregulation, JNK activation and increased cellular motility. Thus, HEF1 induction might be responsible of EMT(Epithelial Mesenchymal Transition)-associated processes. Other AhR-related regulatory pathways might be involved in those phenomena including regulation of Slug or TGFbeta signaling pathways.

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