Adipose Tissue Pollutants And Obesity

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Summary

During the last decades there has been a dramatic increase in obesity world-wide. There are several reasons for such an increase, including diet and lifestyle. Recently toxicological and epidemiological evidence pointed to a likely contribution of environmental pollutants which has led to the obesogen concept. Perinatal exposure to several endocrine disruptors leads to increased body weight later in life as well as to several metabolic disorders, which may partially contribute to the obesity epidemics and interact with other risk factors. Additionally, there is evidence that pollutants such as persistent organic pollutants (POPs) trigger an inflammatory phenotype in the adipose tissue (AT) thereby enhancing the pathological consequences of obesity. The AT also plays a role in the toxicokinetics of POPs since it can store these chemicals for a long time and, in that sense, may be protective during acute exposure. However growing evidence suggests that these chemicals can be released from the AT at a low level. Thus, this tissue constitutes an endogenous source of chronic exposure to POPs.

Introduction

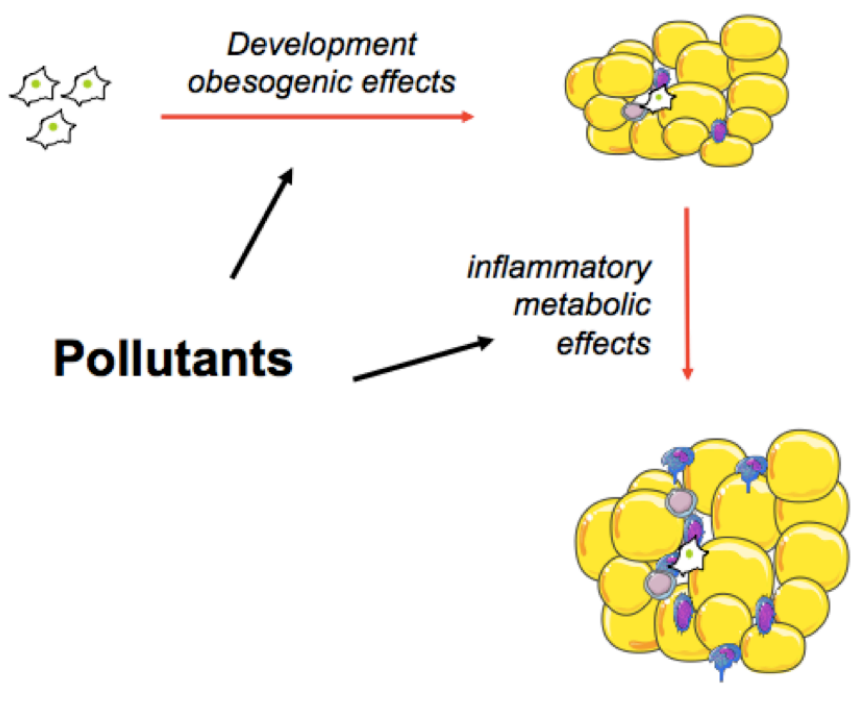
Non-communicable diseases have considerably increased worldwide during the last decades (1). The increase in obesity prevalence is particularly relevant since it is a commonly known risk factor for disorders such as impaired glucose tolerance, metabolic syndrome, diabetes mellitus, liver and cardiovascular diseases (CVD), as well as some cancers (2). The adipose tissue (AT) of obese individuals is quantitatively much larger and includes more pathological features, than that of lean individuals. Much of our understanding of the interaction between obesity and environmental pollutants is largely focused on the AT. Historically, the AT was considered as a simple storage tissue. However, its physiological functions have been considerably reassessed over the last decade (3). Evidence for metabolic, endocrine and immune functions of the AT including stroma has accumulated. Greater attention is now given to the pathological contribution of the AT to obesity and metabolic disorders such as type 2 diabetes. Lately, various interactions between the AT and certain pollutants such as the persistent organic pollutants (POPs) have been established suggesting that this tissue plays a significant role in the kinetics and the toxicity of POPs.

This review will summarize recent observations on the interaction of POPs with AT and obesity (for more details, refer to 4, 5). POPs cannot be metabolized by the xenobiotic metabolizing system and therefore tend to accumulate in ecosystems and in living organisms. The best studied are those which were listed in the Stockholm convention to limit their production and dissemination because of their possible long term toxicity (5, 6). POPs include certain organochlorine pesticides, dioxins, furans, polychlorobiphenyls and polybrominated flame retardants. They do not readily undergo degradation by xenobiotic metabolizing enzymes (XMEs), because of their bulk and halogenation. However, they do activate certain xenobiotic receptors, and some bind to certain XMEs such as CYP1A2 without undergoing catalytic transformation. Because of their hydrophobicity, POPs tend to distribute into lipid rich tissues such as the AT and milk.

We can now consider that, in addition to its other metabolic and endocrine functions, the AT has an identified and diverse toxicological function. First, the AT is a target of several chemicals which alters its functions, increase inflammation, and/or modulate the differentiation of precursor cells. For instance, obesogens are exogenous chemicals (food contaminants, pharmaceuticals, personal care products, or environmental toxicants) that directly or indirectly increase obesity through disruption of metabolic, hormonal, or developmental processes (7,8). Second, the AT can store a variety of hydrophobic xenobiotic chemicals, in particular POPs. Third, AT also constitutes a low-grade internal source of stored POPs leading to continuous exposure of other tissues. In this review, we discuss the interaction between pollutants and obesity with a focus on the complex, previously unsuspected, role of AT in toxicology.

The Obesogen Concept

Exposure to certain pollutants during particular windows of vulnerability has been shown to increase AT mass and contribute to obesity later in life. Development, e.g. prenatal, postnatal, and pubertal, is likely a critical window of susceptibility to obesogen effects of toxic exposures (9) (figure 1). Programming mechanisms are still unclear (see below), but are believed to involve epigenetic regulation of critical genes that lead to adiposity later in life (10, 11). Evidence suggests that developmental exposures to chemicals that increase risk of obesity sometimes operate in a non-monotonic dose-response manner; cachexia may occur at high doses whereas body and/or adipose mass gain occurs at low doses of the same chemical. Further, there may be gender specific effects of developmental toxic exposures that increase the risk of obesity (12). Developmental exposures to these same POPs are positively associated with obesity in humans (4, 5).



<u>Figure 1:</u> Model representing the effect of pollutants on AT. *Exposure to several chemicals called obesogens during the perinatal period leads to the development of obesity later in life. The mechanisms of this programing effect have not been delineated, however, it is believed that epigenetic regulations are involved. Pollutants, particularly POPs, can also interfere with AT biology either by increasing* *inflammation or through metabolic disruption and thereby contribute to the appearance of pathological side effects of obesity. Such mechanisms may also take place at the adult stage and are therefore distinct from the obesogen effects.*

Obesogens are frequently endocrine disruptors and belong to several chemical families. Several studies have been carried on POPs which are either dioxin-like (DL), ie they mimick the effect of dioxin on the dioxin receptor, AhR, or non DL. Rodent models indicate that DL chemicals may be obesogens. Exposure to TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin), 100 µg /kg b.w. once every 2 weeks for 8 weeks, increased body weights of adult mice over 40% higher than control-treated C3H/HeN mice (13). This body weight change was only seen when mice were fed a high fat diet. In a one-month study, chronic developmental exposure to the PCB mixture Aroclor 1254 was associated with increased body weights of mouse pups on postnatal days (PND) 16-20 (14). Further, exposure of adult mice PCB-77 led to an AhR dependent increase in body mass (15). This PCB-77 exposure also increased fatty liver in CVD model mice (16). Fatty liver, attributed to increased hepatic triglycerides and cholesterol, was also caused by 50 mg of PCB-169/kg body weight (17).

There is limited evidence of increased adiposity in animal studies of POPs that are not DL, however body fat is seldom assessed in studies reporting no increased body mass after POP exposure (9). Prenatal exposure to a major polybrominated- diphenyl ether (PBDE-99, 2,2',4,4',5-penta-BDE) increased mouse birth weight (18), and pre- and postnatal exposure to BDE-47 (2,2',4,4'-tetra-BDE) increased rat body weights from birth to puberty (when the study ended) (19). In the longest study of developmental PBDE exposure to examine body weights, male mice exposed to BDE47 10 days after birth had increased body weights from PND 47 until the end of the study, at 4 months of age (20). These studies indicate significant body composition effects of perinatal exposure to PBDEs, however the mechanisms remain unclear and the data should be interpreted with caution as certain preparations of BDEs could be contaminated with DL chemicals. In perinatal exposure to perfluorooctanoic acid (PFOA) which is not a traditional POP, obesogenic effects do not appear until later in life. Mice exposed to low levels of PFOA in utero had increased body mass once mature, with an inverted U shape dose response curve (21). By 18 months of age, there was no longer an effect on mouse weight, however, there was a positive dose response relationship between in utero PFOA exposure levels and abdominal brown AT mass in the aged mice, whereas a negative relationship was found with white AT mass. Consistent with experimental findings, a recent prospective human study demonstrated that maternal PFOA levels during pregnancy were associated with obesity in the daughters 20 years later (22). Organochlorine pesticides may also increase adiposity. For instance, oral DDT exposure increased the body weights and/or adiposity of both mouse and rat offspring in several multi-generational studies (11, 23, 24).

Several studies assessing obesogenic effects were devoted to other pollutants which are not persistent, particularly endocrine disruptors. Much effort was devoted to Bisphenol A (BPA), and, in many cases, perinatal exposure to BPA was shown to lead to increased body weight later in life (reviewed in 25 and 26). Non monotonic curves were sometimes observed. However, the effect of BPA was not always consistent, suggesting that specific experimental conditions were required to unravel the obesogenic effects of BPA. This could be interpreted as suggesting that the interaction of this chemical with other environmental factors such as diet is critical for the obesogenic effect to be observed. Human studies recently demonstrated that fetal exposure to BPA was associated with increased BMI in 4 years old children (27). Another well studied obesogen is tributyltin (TBT). Perinatal exposure to TBT leads to increased adipose mass transgenerationally (28, 29). These effects have been related to the activation by TBT of the PPARg/RXRa heterodimer and with a possible involvement of epigenetic effects. The effects of more complex exposures such as maternal smoking and air pollution, which also correlate with offspring obesity, will not be discussed here.

Are metabolic consequences of obesity induced by pollutants?

Obesity causes predisposition for other metabolic diseases such as type 2 diabetes and and metabolic risk features such as moderate elevation of glycemia, hypertriglyceridemia or low HDL. Several epidemiological studies carried following industrial exposure of workers or accidental contamination by POPs indicated a relationship between serum concentration of certain POPs and markers of diabetes or of a prediabetic state. This is the case of the Seveso cohort in which increased metabolic syndrome (but not obesity) was observed in women exposed to dioxin before the age of 12 (30). Such a correlation was also found in a large study carried in the general population (31). Prospective studies in the elderly have also indicated a possible role of certain POPs in the pathogenesis of type 2 diabetes (32). There are also some experimental studies clearly correlating POP mixtures with metabolic syndrome occurrence in the rat (33). A National Toxicology Program workshop concluded that POPs were associated with type 2 diabetes but that no causal relationship could be established at this stage (34). A recent study indicated that metabolically healthy but obese individuals had lower plasma levels of several classes of POPs than obese individuals with metabolic abnormalities (35). Other pollutants were also associated with metabolic diseases but only POPs have been discussed here.

The interactions between obesity, POPs and metabolic disruption were unraveled in several mechanistic studies. Because of the implication of the AT in metabolic diseases, it was hypothesized that this tissue could be a target of POPs and indeed, several effects were found. Its vulnerability may be due to its ability to accumulate POPs as we will see later. Most of the studies were in vitro or ex vivo, but recently the effect of POPs on the AT of rodents was also assessed. POPs were shown to display anti-insulin effects in cellular models of adipocytes. For example, dioxin repressed the glucose transporter Glut4 expression and lipoprotein lipase in 3T3-F442a cells (36). This anti-insulin effect is not general and consistent for all genes. Indeed, whereas dioxin was found to antagonize insulin action on certain genes such as the IGFBP1 gene in hepatocytes (37), it displayed a different effect on other genes such as the liver PEPCK gene, since it tended to inhibit gluconeogenesis in this tissue, similarly to insulin (38).

Inflammation of the AT is one of the hallmarks of obesity and inflammatory phenotype is critical in metabolic diseases. POPs have been shown to induce proinflammatory genes in rodent adipose cells (36). We found similar effects in human adipocytes (39). Importantly, in mice treated with dioxin, not only the gene expression of proinflammatory genes was increased, but also invasion of this tissue by macrophages and lymphocytes was observed (39). Finally, dioxin was shown to inhibit the differentiation of adipocyte precursor cells in certain model systems and to antagonize the effects of PPARg. However the actual mechanisms remain elusive (40). In conclusion, preadipocytes and adipocytes are targeted by POPs which appear to disrupt certain signaling and differentiation pathways and to induce inflammation.

Is there a protective role of AT and obesity?

As mentioned earlier, the AT is a compartment which contains a high amount of POPs, particularly in organisms that are at the top of the food chain. Such a bioaccumulation leads to the age-dependent increase in POP content (41). POPs are taken up by adipocytes and localize within lipid droplets (42). However their precise location and their actual effects at the subcellular level are poorly understood. It is nevertheless believed that their accumulation within the AT decreases their availability for other cells and tissues thereby limiting their toxicity. Experimental evidence supports such a protective function for the AT. Indeed, studies carried in the 80s and the 90s showed that there was an inverse correlation between toxicity of POPs and fat mass of different animal species. Authors compared the 30-day toxicity of TCDD in approximately twenty terrestrial animal species and found a positive correlation between the BMI of these species and the LD50 (the dose that leads to 50% death in the animal population) of dioxin (43). They concluded that the species with the highest fat mass tended to display better resistance to dioxin in this particular acute exposure test. These conclusions were in line with studies showing that resistance of aquatic species to dioxin was also related to their fat mass leading to the paradoxical notion of "survival of the fattest" (44). However, these observations should not be taken as evidence suggesting that the BMI is the only factor discriminating sensitive and resistant species. There is indeed strong evidence for a major contribution of the genetically determined arylhydrocarbon receptor affinity for dioxin.

It should be stressed that this protective function of the AT was revealed in acute or subacute exposure tests. These high dose treatments may allow the distribution of the pollutants to all tissues unless an efficient "filter" or a buffer system can capture them, thereby decreasing exposure of the most sensitive tissues. This role is played by the partitioning of POPs into lipid-rich tissues. This kinetic protective system does not only include the AT. Indeed, it has been established that proteins such as the dioxin-inducible liver CYP1A2 can bind this pollutant particularly during acute or subacute exposures and play an important role in its toxicokinetics (45). It is now believed that POPs are first distributed throughout the body and then captured by the liver inducible protein compartment, with excess then redistributed to the AT. Obviously, these kinetic distribution mechanisms depend heavily on the treatment dose and the body burden (46). Furthermore, in several metabolic disorders, lipid droplets are found in other tissues such as liver, muscle, heart, etc. with possible consequences related to POP storage.

AT could also be involved in the higher blood half-life of POPs in children. Indeed, newborns have a high body burden due to placental transfer during pregnancy and to breast-feeding. A higher blood elimination rate observed for the children compared to the adults might be explained by the dilution of the POPs across tissues like the AT rather than a higher metabolic rate.

There is some indirect evidence for a protective role of AT from human studies. The association between fat mass and mortality depends on the serum concentration of POPs. Indeed, in those individuals with low POP concentration, mortality increased with fat mass, whereas in those with high POP concentrations, mortality tended to paradoxically decrease with fat mass (47). These observations can be accounted for by a protective function of the AT which becomes significant at high levels of POP contamination.

Is the AT a source of endogenous exposure?

As mentioned earlier, POPs and other lipophilic contaminants distribute according to their affinity for proteins and lipids and are stored primarily in the liver and the AT. They are also found in blood from which they can contaminate other tissues. Blood POP content can be either related to their release from storage tissues or to recently absorbed pollutants. Several observations in both human and animals suggest that the release of pollutants from the AT is an important source of blood POPs.

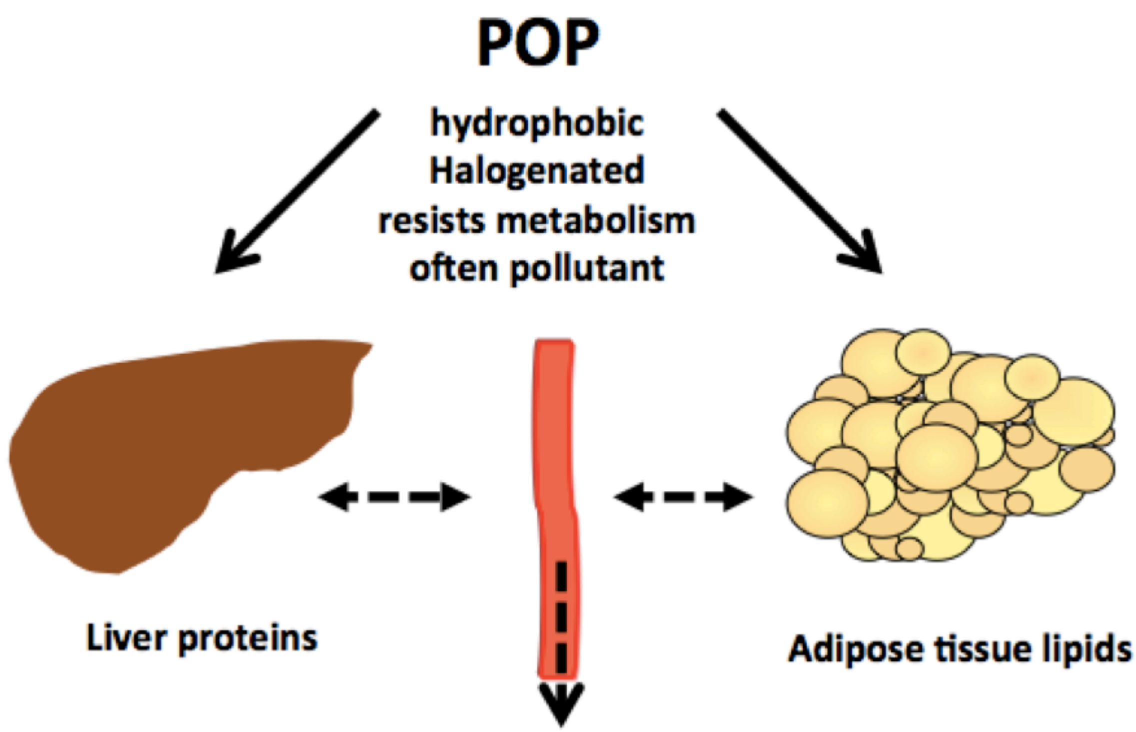
In humans, most of the evidence has been gathered from studies on drastic weight loss in obese individuals. Such a weight loss can be achieved voluntarily through diet and bariatric surgery and could lead to a decrease of up to 30 kg of fat mass or even more in some cases. Several independent studies have shown that there was an increase in blood POPs following fat mass loss elicited by either diet alone or diet coupled with bariatric surgery (48, 49). If increased blood POP levels during weight loss is related to their release from AT, one would expect changes in POP content of this tissue. This has been addressed by Kim et al (49) who determined POP concentrations in both blood and AT and who also assessed the total amount of fat in the studied individuals. The data indicate that POP concentration in AT (expressed per gram lipid) increases with weight loss. While this may seem paradoxical, it is not particularly surprising since the total amount of fat mass decreases considerably thereby leading to an increased concentration of pollutants, e.g. released POPs can be taken up readily by the remaining fat. In line with these suggestions, we observed that POP concentrations in the AT of obese individuals is lower that that of lean individuals. However, the total amount of fat-stored POPs is 2- to 3-fold higher in obese individuals as compared to lean controls. Furthermore, this total amount tends to decrease by 15% following weight loss at least for certain POPs. This observation suggests that there is indeed some degree of POP release from AT during weight loss and that this release leads to a moderate decrease in total POP content.

Experimental evidence also suggests redistribution of POPs from their storage sites in the AT. Indeed, a study shows that in rodents pretreated with radiolabeled hexachlorobenzene, weight loss leads to a time-dependent increase in the brain content of this compound (50). The study shows that weight loss alters the distribution of lipophilic pollutants, thus leading to enhanced localization in the brain and other sensitive tissues with possible toxic outcome.

Observational studies were also carried in northern elephant seals. These animals accumulate a large amount of fat in order to cope with extended fasting. Their fat is contaminated with PCBs. During the fasting period which could last several weeks, they lose a large amount of fat. Debier et al (51) have shown that an increase in serum concentration of PCB during fasting which is likely due to their release from fat depots. Interestingly, the concentration of PCBs also increased in some of these depots (blubbers) because of the decreased fat content. However, different fat depots did not undergo similar changes, suggesting differences in the kinetics of POP exchange and release. It is suggested that the release of POPs during fasting may lead to toxic effects.

A critical issue is whether the release of POPs from AT observed during weight loss could lead to toxic outcomes in other organs and tissues. Indirect evidence was obtained in humans from several studies of weight loss triggered by either diet or diet associated with bariatric surgery. We have shown that the dynamic increase in serum POPs following drastic weight loss correlated with a delayed and reduced improvement of blood lipid parameters and liver toxicity biomarkers (49). Correlations between blood POP concentrations and other clinical parameters such as metabolic and muscle parameters, were also observed in humans by the group of Tremblay who conducted seminal studies in this field (52).

Conclusion and Hypothesis



<u>Figure 2:</u> Fate of a persistent organic pollutant (POP). *Most xenobiotics are metabolized primarily by the liver and are thus detoxified. The detoxification system tends to render hydrophobic xenobiotics more hydrophilic which leads to their elimination in urine. Several halogenated xenobiotics are not metabolized and therefore tend to bind to liver proteins and to adipose mass. They can thus persist for years in the body and constitute a putative long term threat since they can be released from these compartment at low levels.*

The AT appears to play critical roles in the kinetics of POPs and in their pathogenic effects. It has a major role, together with the liver protein compartment in storing POPs and in preventing their distribution into more sensitive tissues. However, the AT storing capacity is constitutive and not inducible. This kinetic system acts as a buffer during acute or subacute exposure conditions. However, it translates an acute exposure into a long term, low-grade internal exposure (see figure 2). It thus transforms an immediate threat into a latent chronic threat. This buffer system perfectly illustrates a previously developed hypothesis (53) which proposes that systems that protect from acute exposure to xenobiotics contribute to their chronic toxicity. In addition to these functions, the AT constitutes a target of POP toxicity. Indeed, the main toxic effect triggered by these compounds is inflammation which is a well known risk factor for metabolic diseases. These observations support the contribution of POPs to metabolic diseases and suggest that AT alteration could at least partially mediate these effects.

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51. Barouki R Linking long-term toxicity of xeno-chemicals with short-term biological adaptation. Biochimie 2010;92:1222-6.
52. La Merrill M, Birnbaum LS. Childhood obesity and environmental chemicals. Mt Sinai J Med 2011;78:22-48

~ About the Authors ~

Robert Barouki

Robert Barouki is a biochemist and molecular biologist whose main research focus during the last fifteen years has been understanding the mechanisms of toxicity of environmental pollutants such as dioxin. In particular, he has studied the biological consequences following the activation of the dioxin receptor AhR. He studied the different effects triggered by different ligands of the AhR using in particular "-omics" technologies, suggesting that part of the toxicity may be related to the disruption of endogenous functions.

In addition, as head of the clinical metabolic biochemistry department, he has initiated and organized a shared mass spectrometry facility at the Necker hospital. His focus is on developing multiplex targeted proteomic and metabolonomic assays, notably in the field of metabolic diseases and in pharmacodynamics.

Education/Training

1983 – University of Paris 5, France; Medicine (MD)
1982 – Ecole Normale Supérieure Ulm, France; Biochemistry Pharmacology
1982 – University of Paris, France; Pharmacology (Ph.D.)
1986 – Johns Hopkins Medical School; Molecular biology (Post-doc)
1992 – University of Paris, France; Pharmacology (Habilitation)

Positions and Employment

1984-1986 - Post-doctoral Fellow at the Department of Molecular Biology of the Johns Hopkins Medical School in Baltimore (Pr Hamilton O Smith)
1983-1992 - Research scientist, CNRS, Inserm unit 99, Créteil France
1992-2001 - Director of Research, Inserm, Inserm unit 99, Créteil France
2001-Present - Professor, University Paris Descartes, Paris, France
2005-Present - Director of unit 1124 Inserm (Pharmacology Toxicology and Cellular Signaling) at the University Paris Descartes
2012- present - Head of the clinical Metabolomic and Proteomic Biochemistry Department at the Necker Enfanst maladies hospital.

Honors

1983 – Award from the French society of Endocrinology –
1984 – Fellowship Award from the EMB
2004 – Member of the scientific council of Université Paris Descartes
2007 – Member of the Inserm scientific council
2010 – Member of the Anses (Environment and food agency) scientific council
2010 – Head of the ANR (national research agency) study committee on toxicology and

ecotoxicology

2011 – Member of the expert committee of the French institute of public health (environmental issues)

Selected Peer-reviewed Publications (Selected from ~100 peer-reviewed publications)

1. Diry M, Tomkiewicz C, Koelhe C, Coumoul X, Bock KW, Barouki R, Transy C. Activation of the dioxin/arylhydrocarbon receptor modulates cell plasticity through a JNK-dependent mechanism. Oncogene, 2006; 25: 5570-5574 . Epub 2006 Apr 17. PMID:16619036
2. Barouki R, Coumoul X, Fernandez-Salguero PM. The aryl hydrocarbon receptor, more than a xenobiotic-interacting protein. FEBS Lett. 2007;581:3608-3615. Epub 2007 Mar 30. Review. PMID: 17412325
3. Bui LC, Tomkiewicz C, Chevallier A, Pierre S, Bats AS, Mota S, Raingeaud J, Pierre J, Diry M, Transy C, Garlatti M, Barouki R, Coumoul X. Nedd9/Hef1/Cas-L mediates the effects of environmental pollutants on cell migration and plasticity. Oncogene. 2009 Oct 15;28(41):3642-3651. PMID: 19648964
4. Barouki R, Coumoul X. Cell migration and metastasis markers as targets of environmental pollutants and the Aryl hydrocarbon receptor. Cell Adh Migr. 2010 Jan;4(1):72-76. PMCID: PMC2852561
5. Ambolet-Camoit A, Bui LC, Pierre S, Chevallier A, Marchand A, Coumoul X, Garlatti M, Andreau K, Barouki R, Aggerbeck M. 2,3,7,8-tetrachlorodibenzo-p-dioxin counteracts the p53 response to a genotoxicant by upregulating expression of the metastasis marker agr2 in the hepatocarcinoma cell line HepG2. Toxicol Sci. 2010 Jun;115(2):501-512. PMID: 20299546
6. Kim MJ, Marchand P, Henegar C, Antignac JP, Alili R, Poitou C, Bouillot JL, Basdevant A, Le Bizec B, Barouki R, Clément K. Fate and complex pathogenic effects of dioxins and polychlorinated biphenyls in obese subjects before and after drastic weight loss. Environ Health Perspect. 2011 119:377-383. Epub 2010 Dec 3. PMCID: PMC3060002
7. Barouki R. Linking long-term toxicity of xeno-chemicals with short-term biological adaptation. Biochimie. 2010 ;92 :1222-1226. Epub 2010 Feb 25. Review. PMID:20188785

Additional recent publications of importance to the field (in chronological order)

1. Massaad, C., Barouki. An assay for the detection of xenoestrogens based on a promoter containing overlapping EREs. Environ. Health Perspect., 1999, 107: 563-566. PMCID: PMC1566659
2. Coumoul, X., Diry, M., Robillot, C., Barouki R. Differential regulation of CYP1A1 and CYP1B1 by a combination of dioxin and pesticides in the breast tumor cells MCF-7. Cancer Res, 2001, 61: 3942-3948. PMID:11358810
3. Bonvallot, V, Baeza-Squiban, A, Baulig, A, Brulant, S, Boland, S, Muzeau, F, Barouki, R, Marano, F. Organic compounds from Diesel exhaust particles elicit a proinflammatory response in humann airway epithelial cells and induce CYP1A1 expression. Am J Respir Cell Mol. Biol, 2001, 25: 515-521. PMID:11694458
4. Coumoul X, Diry M, Barouki R. PXR-dependent induction of human CYP3A4 gene expression by organochlorine pesticides. Biochem Pharmacol 2002;64:1513-1519. PMID:12417264
5. Gouedard C, Barouki R, Morel Y. Dietary polyphenols increase paraoxonase 1 gene expression by an aryl hydrocarbon receptor-dependent mechanism. Mol Cell Biol 2004;24:5209-5222. PMCID: PMC419885

6. Marchand A, Tomkiewicz C, Marchandeau JP, Boitier E, Barouki R, Garlatti M. 2,3,7,8-tetrachlorodibenzo-p-dioxin induces insulin-like growth factor binding protein-1 gene expression and counteracts the negative effect of insulin. Mol Pharmacol 2005; 67:444-452. PMID:15496506
7. Baulig A, Singh S, Marchand A, Schins R, Barouki R, Garlatti M, Marano F, Baeza-Squiban A. Role of Paris PM(2.5) components in the pro-inflammatory response induced in airway epithelial cells. Toxicology. 2009 Jul 10;261(3):126-135. PMID:19460412
8. Diana J, Griseri T, Lagaye S, Beaudoin L, Autrusseau E, Gautron As, Tomkiewicz C, Herbelin A, Barouki R, Von Herrath M, Dalod M, Lehuen A. NKT Cell-Plasmacytoid Dendritic Cell Cooperation via OX40 Controls Viral Infection in a Tissue-Specific Manner. Immunity. 2009 30:289-299 Epub 2009 Feb 12. PMID:19217323

Selection of Research Supports

<u>Ongoing Research Support</u>

Constitutive Grant from Inserm and Université Paris Descartes for unit 747

As a head of an Inserm-Université Paris Descartes unit (unit 747), I receive significant yearly support from these institutions. The grant is based on the general proposal of the unit. The unit includes 5 teams (80 people), my own being the largest one and receives approximately one fourth of the unit support. The grant partially funds all our projects including those dealing with effects of dioxin in several models studied by omics technology, the interaction between pollutants, the structure of pollutant receptors as well as studies on the toxicity of alcohol and drugs. This grant represents approximately 40% of our budget.

Role: Principal Investigator`

Heals: FP7 EU grant (2013-2018)

The aim of the project is to provide molecular and cellular mechanisms of contaminant action in the context of a consortium working on human exposome.

Co-investigator

PHRC grant calcilung : (2014-2017)

pharmacodynamics of immunosuppressive drugs in lung transplantation

Co-investigator

PlasticAhR (2011-2014)

ANR (National Research Agency)

The aim of this project is to obtain a crystal structure of the dioxin receptor AhR. The structure of this receptor has not been determined yet. It would allow a better assessment of the mechanisms of ligand binding. Modeling should allow prediction of binding to this receptor, an important issue for predictive toxicology. The principle investigator, Dr P Nioche, is a member the Inserm unit 747 that I chair.

Role: co-Investigator

Other grants: oncometabotox (persistent organic pollutants and metabolism), Metapop (pollutants in adipose tissue and cancer), Hepatodiox (combined effects of pollutants and nutrients on liver toxicity), Allofattox (role of adipose tissue in POP toxicokinetics), ToxAhrBrain (role of the Ah Receptor in brain functions), calcilung (VLM: calcineurin in lung transplantation)

Completed Research Support

Nemo (2009-2012)
Ineris
The aim of this project is to identify cellular and reporter systems to determine biological effects of AhR in human and zebrafish
Role: co-Investigator

AhR ligands (2009-2012)
Anses (agency for food and environment)
The aim of the project is to implement various reporter systems that can distinguish between the various biological effects of AhR ligands. The principle investigator, Dr X Coumoul, is a member the Inserm unit 747 that I chair.
Role: co-investigator

OncoPOP (2006-2010)
ANR (National Research Agency)
The ailm of that project was to study the effects of AhR ligands on epithelial mesenchymal transition, to identify the proteins that mediate these effects, to carry a proteomic analysis and to establish animal systems to assess the possible effects of AhR ligands on cancer metastasis.
Role: Principal Investigator

Adipotox (2006-2010)
ANR (National Research Agency)
This project allowed us to identify the effect of dioxin and persistant organic pollutants on adipose tissue differentiation and inflammation. It also allowed to study the consequences of drastic weight loss on the distribution of these pollutants, on their effects on gene expression and on the possible correlation with disease markers.
Role: Principal Investigator

Pollutant interaction (2006-2008)
Anses
The project aimed to study the cross talk between dioxin and an organochlorine pesticide, endosulfan at the cellular level.
Role: Principal Investigator

Jean-Philippe Antignac

Dr. Jean-Philippe Antignac is engineer and PhD graduated in analytical chemistry, and a scientist belonging to the National Institute of Agronomic Research (INRA). He is since 2007 the scientific officer of LABERCA, which is a research Unit working in the areas of chemical food safety and environmental health. He is also contributing to public expertise working groups for INSERM and the French Food Safety Agency (ANSES). His competence areas are the analysis of organic chemical residues and contaminants in biological matrices for risk assessment and environmental health purposes. His specific research field is the study of endocrine disrupting chemicals from a human exposure assessment point of view. Through various collaborations he is also involved in several projects studying the relation between this human environmental chemical exposome and reproductive and developmental functions or hormono-dependent cancers. The development and application of global chemical phenotyping approaches such as metabolomic or lipidomic is another component of his research activities for identifying biomarkers and/or biological signatures associated to a given exposure or a given effect. His is author or co-author of 109 publications in international peer review journals and his current h-index is 28.

Claude Emond

Dr. Claude Emond is a Clinical Assistant Professor in the Department of Environmental and Occupational Health at the University of Montreal, Canada, and Associate Professor at the Institute of Environmental Sciences (ISE) at the University of Quebec in Montreal (UQAM). In this capacity, Dr. Emond delivers lectures in Toxicology classes at the university and supervises graduate students. He received a bachelor's degree in Biochemistry from the University of Montreal in Quebec in 1987, a master's degree in Environmental Health from the University of Montreal in 1997, and a Ph.D. in Public Health (Toxicology and Human Risk Assessment option) in 2001 from the University of Montreal. From 2001 to 2004, Dr. Emond received grants from the National Research Council, a branch of the National Academy of Sciences (NAS), to perform postdoctoral studies for 2½ years at the U.S. Environmental Protection Agency (EPA) in North Carolina. At EPA, Dr. Emond's work focused on describing a developmental physiologically based pharmacokinetic (PBPK) model on dioxins. His research and consulting interests address problems in toxicology and focus on different chemicals, including polychlorinated biphenyls (PCBs), dioxins, flame retardants (polybrominated diphenyl ether [PBDE] and hexabromocyclododecane [HBCD]), bisphenol A, pyrethroid, and xenoestrogens. Dr. Emond's research interests also focus on the development and the improvement of mathematical PBPK models to address and reduce the uncertainty for toxicology risk assessment in human health. Much of his research activities focus on the toxicokinetic and dynamic effects to further characterize the mode of action between chemicals and biological matrices for individuals or populations. He is also interested in occupational toxicology, mainly on the effects of organic solvents, modeling physiological changes in aging compared to younger workers, and nanotoxicology. Dr. Emond recently served on EPA's Science Advisory Board Reviewing Committee for Trichloroethylene (TCE). His expertise was recognized and used in the dioxin reassessment by EPA's National Center for Environmental Assessment. In 2008, Dr. Emond and colleagues founded an international nanotoxicology group called The International Team in Nanotoxicology (www.TITNT.com), which includes collaborators from five different countries. He also recently founded a Delaware-based consulting company called BioSimulation Consulting Inc., which provides services in pharmacokinetics for government by offering analytical data-mining support. He is President of an Endocrine Disruptor Review Work Group for the French Agency for Food, Environmental, and Occupational Health and Safety (ANSES). HeDr. Emond has published many papers and is often invited to present his research at international meetings on persistent organic chemicals and nanotechnology because his work contributes to the improvement of health, safety, and environmental assessment and regulations.

Karine Clément

Prof Karine Clément is full professor of Nutrition, Division of Cardiometabolism, Pitié-Salpêtrière university hospital, Paris 6 Pierre et Marie Curie university, Paris. Since 2011, she is director of the Institute de CardiometAbolism and Nutrition (ICAN) dedicated to innovative Care, Research and training in the field of Cardiology and metabolic diseases. This institute aims at developing personalized medicine in the field of cardiometabolic diseases. During her MD, PhD in Endocrinology, metabolism and Nutrition, she has been involved in genetic and functional genomics aspects of human obesity. Her work led to the identification of monogenic forms of obesity (Leptin receptor and MC4R mutations) and to genetic risk factors in common obesities. Then, she performed a post-doctoral fellowship at Stanford University, CA, USA where she acquired competencies in gene profiling approaches applied to complex diseases (1999-2000), and in 2001, obtained a "Avenir" INSERM team before the creation of an INSERM/UPMC called NutriOmics "Nutrition and obesity Systemic approaches"; grouping different expertise (metabolism, nutrition, physiology, bioinformatics). She contributed to more than 250 international publications, reviews and many international conferences in the field (h-Index 61). Her research team showed notably that inflammatory and remodeling genes (i.e. profibrotic genes) in human adipose tissue are modulated by weight variation in parallel to changes in immune cells. The team was the first to demonstrate the accumulation of fibrosis in human adipose tissue. Deeper insights into mechanisms have been undertaken by exploring cross-talks between adipose and stroma-vascular cells (immune and non immune) and between adipocytes/ adipose tissue and muscle cell/ atria. Her research team is exploring the link between environmental changes, systemic changes and functional modifications in the adipose tissue. Many clinical studies are conducted in her group particularly in bariatric surgery model. The gut microbiota is of evidence a key actor of this link. She is a member and expert of several national and international scientific committees in obesity and metabolism and contributes to several European Networks in genetics and functional genomics (Diogenes, Hepadip, ADAPT, FLIP and coordinates METACARDIS at INSERM). Web site: http://www.ican-institute.org/team/umr_s872team-7-nutriomics-nutrition-obesity-systemic-approaches/

Linda Birnbaum

Linda S. Birnbaum, Ph.D., is director of the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health, and the National Toxicology Program (NTP). As NIEHS and NTP director, Birnbaum oversees a budget of more than $740 million that funds biomedical research to discover how the environment influences human health and disease. The Institute also supports training, education, technology transfer, and community outreach. NIEHS currently funds more than 1,000 research grants.

A board certified toxicologist, Birnbaum has served as a federal scientist for nearly 35 years. Prior to her appointment as NIEHS and NTP director in 2009, she spent 19 years at the Environmental Protection Agency (EPA), where she directed the largest division focusing on environmental health research. Birnbaum started her federal career with 10 years at NIEHS, first as a senior staff fellow in the National Toxicology Program, then as a principal investigator and research microbiologist, and finally as a group leader for the Institute's Chemical Disposition Group.

Birnbaum has received many awards and recognitions. In October 2010, she was elected to the Institute of Medicine of the National Academies, one of the highest honors in the fields of medicine and health. She was elected to the Collegium Ramazzini and to the Institute of Medicine of the National Academies of Science, and received an honorary Doctor of Science from the University of Rochester and a Distinguished Alumna Award from the University of Illinois. Other awards include 2 NIH Director's Award, Women in Toxicology Elsevier Mentoring Award, Society of Toxicology Public Communications Award, EPA's Health Science Achievement Award and Diversity Leadership Award, National Center for Women's 2012 Health Policy Hero Award, Breast Cancer Fund Heroes Award, 2013 American Public Health Association Homer N. Calver Award, 2013 Children's Environmental Health Network Child Health Advocate Award, 2014 Mailman School of Public Health Granville H. Sewell Distinguished Lecturer, an Honorary Doctorate from Ben-Gurion University, Israel, the Surgeon General's Medallion 2014, and 14 Scientific and Technological Achievement Awards, which reflect the recommendations of EPA's external Science Advisory Board, for specific publications.

Birnbaum is also an active member of the scientific community. She was vice president of the International Union of Toxicology, the umbrella organization for toxicology societies in more than 50 countries; former president of the Society of Toxicology, the largest professional organization of toxicologists in the world; former chair of the Division of Toxicology at the American Society for Pharmacology and Experimental Therapeutics; and former vice president of the American Aging Association.

She is the author of more than 700 peer-reviewed publications, book chapters, and reports. Birnbaum's own research focuses on the pharmacokinetic behavior of environmental chemicals, mechanisms of action of toxicants including endocrine disruption, and linking of real-world exposures to health effects. She is also an adjunct professor in the Gillings School of Global Public Health, the Curriculum in Toxicology, and the Department of Environmental Sciences and Engineering at the University of North Carolina at Chapel Hill, as well as in the Integrated Toxicology and Environmental Health Program at Duke University.

A native of New Jersey, Birnbaum received her M.S. and Ph.D. in microbiology from the University of

Illinois at Urbana-Champaign.

Michele La Merrill

Michele La Merrill conducts integrated toxicological and epidemiological studies to understand susceptibility to environmental diseases. These susceptibilities include environmental insults during the exquisitely sensitive developmental period, poor diet and ensuing metabolic diseases, and genetic and epigenetic predispositions. She earned her Ph.D. in Toxicology from the University of North Carolina, Chapel Hill and her M.P.H. in epidemiology during her postdoctoral fellowship at the Mount Sinai School of Medicine. She is an Assistant Professor of Environmental Toxicology at the University of California, Davis where she teaches courses in Toxicology and on Gene x Environment Interaction. She is a member of the IARC Monographs Working Group for volume 113, on some organochlorine insecticides and chlorphenoxy herbicides.

Min Ji Kim

Min Ji Kim studied, during her PhD, the adipose tissue dysfunctions in obesity and antiretroviral therapy-induced lipodystrophies at the University of Paris 6 and at INSERM. These diseases shares some common features among which the low-grade adipose tissue inflammation. During her postdoctoral fellowship at INSERM U747, she studied and determined the pro-inflammatory effects of pollutants which explain a possible contribution of pollutants in the pathogenesis of metabolic diseases.

She is now an Associate Professor at Paris 13 and at INSERM U1124, keep on exploring the obesogen and metabolic effects of pollutants by combining animal and cell models in order to understand the role of environmental factors in the increasing incidence of metabolic diseases.

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