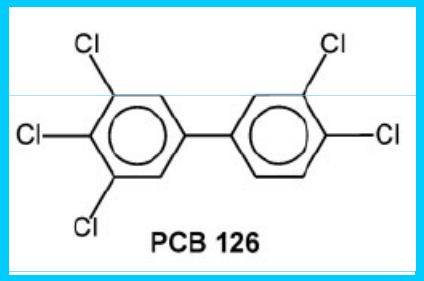
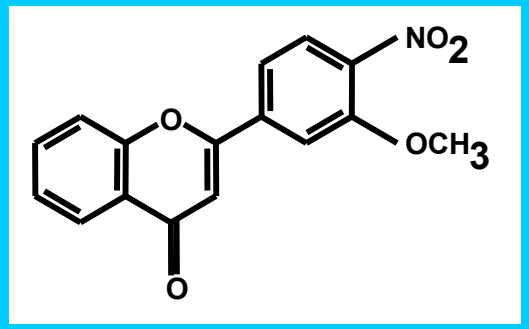
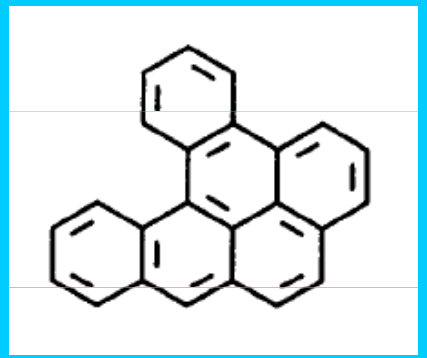
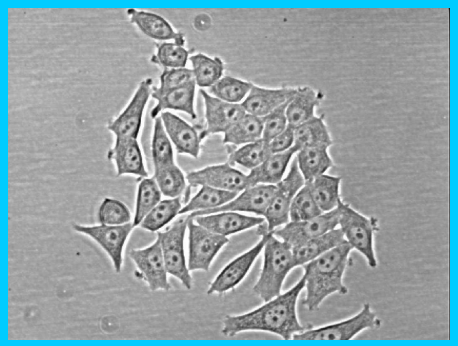
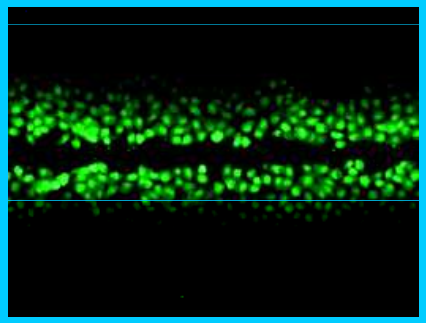
Narušení regulace buněčného cyklu, programované buněčné smrti či mezibuněčné komunikace prostřednictvím organických polutantů – mechanismy karcinogeneze?

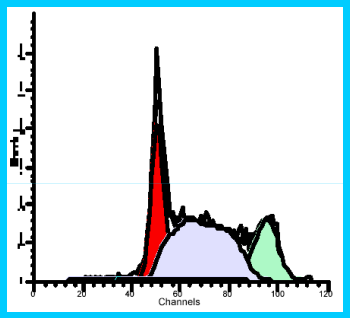


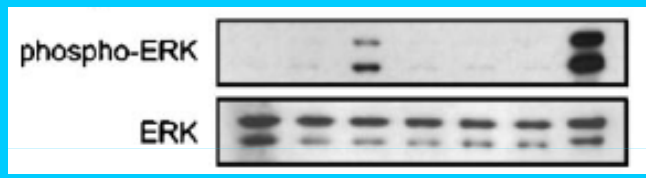


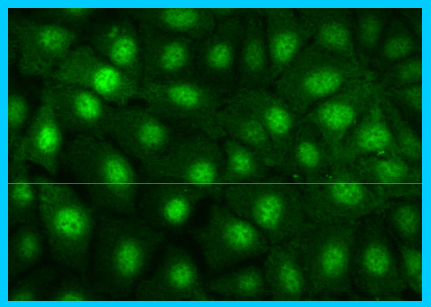


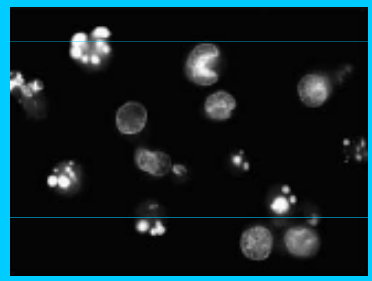




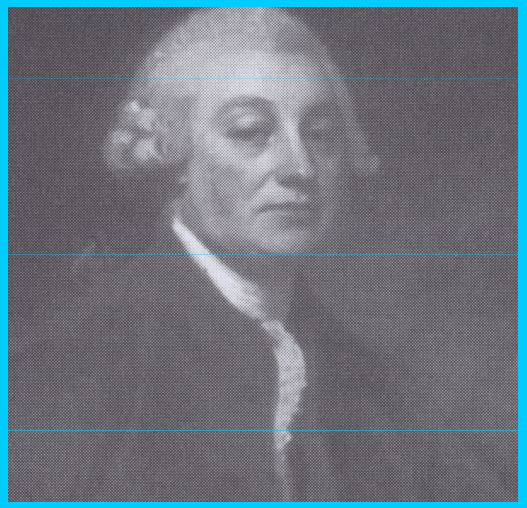






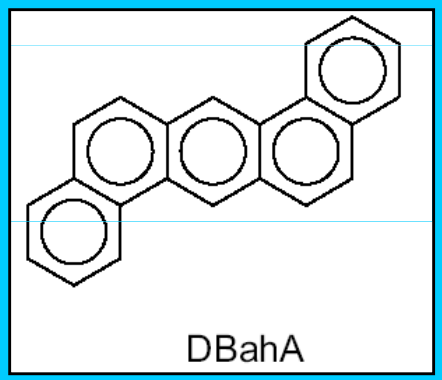


Polycyclic aromatic hydrocarbons (PAHs):

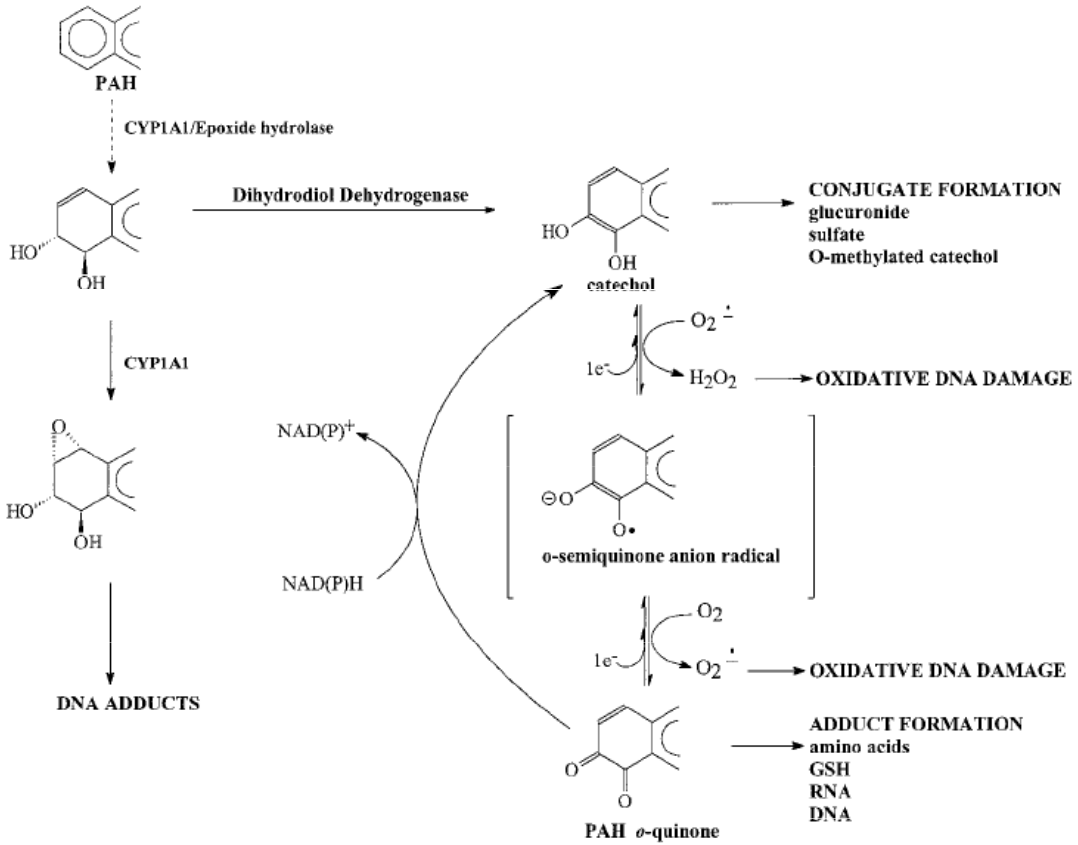


Sir John Percivall Pott (1775):
„first published description of an occupational cancer related to coal soot"

Sir Ernest Kennaway (1931):
„first single PAH carcinogen"



Reality is not so simple:
- **alternative bioactivation pathways;**
- **tumor promoting effects of PAH metabolites;**
- **direct cellular effects of parental compounds;**
- **to describe nongenotoxic effects of POPs, it is necessary to study their mechanisms of effects of at cellular and molecular level.**

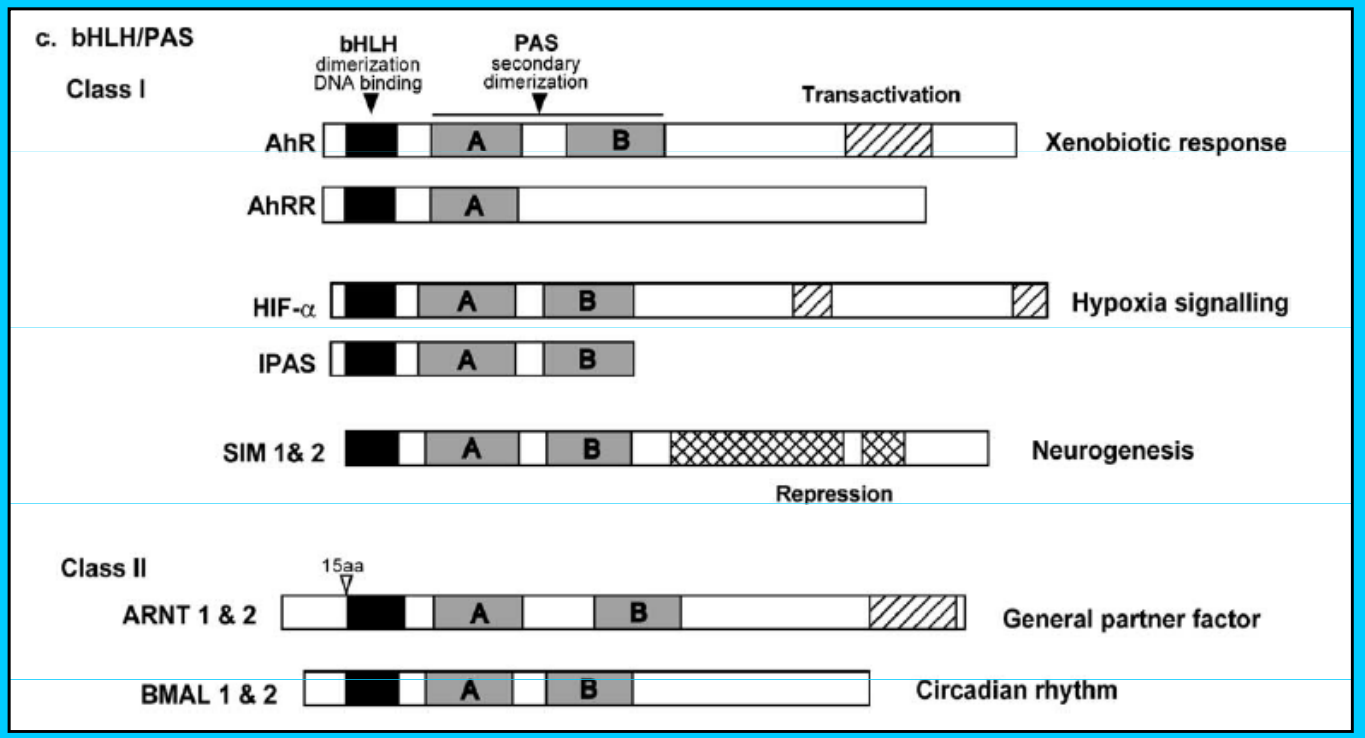


Model chemical carcinogens
vs.
environmental pollutants

Possibilities open for alternative effects of PAHs:

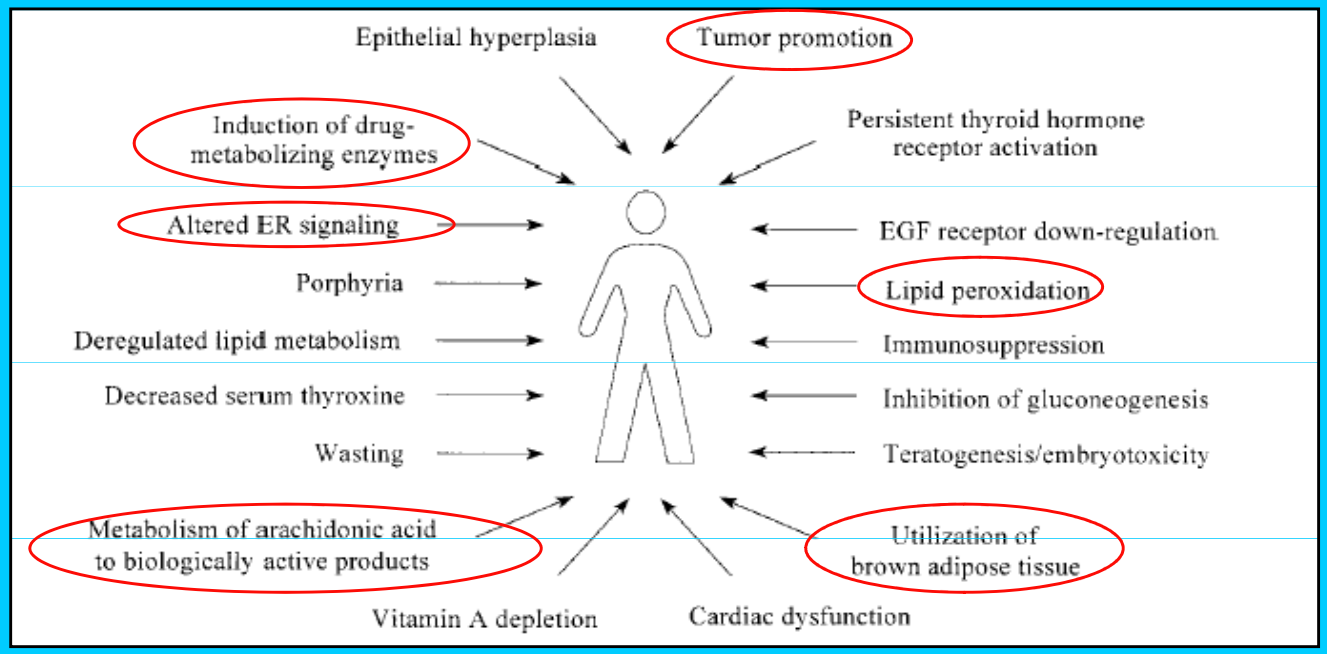
- **direct alteration of signaling pathways (mitogen-activated protein kinases; tyrosine kinases; Ca^{2+}; modulation of phospholipid metabolism)**
- **interation with nuclear receptors (estrogen receptor-α; estrogen receptor-β; androgen receptor; peroxisome proliferator-activated receptors);**
- **deregulation of cell-to-cell communication – gap junctions; adherens junctions;**
- **deregulation of cell proliferation and programmed cell death;**
- **aberrant function of cell cycle checkpoints and DNA repair;**
- **epigenetic effects;**
- **alternative biotransformation and oxidative stress;**
- **activation of the aryl hydrocarbon receptor (AhR) and related effects;**

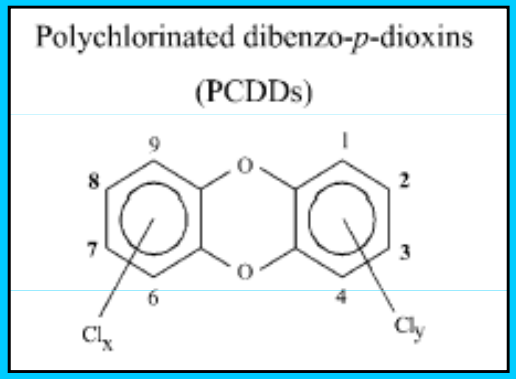
AhR = bHLH-PAS family protein

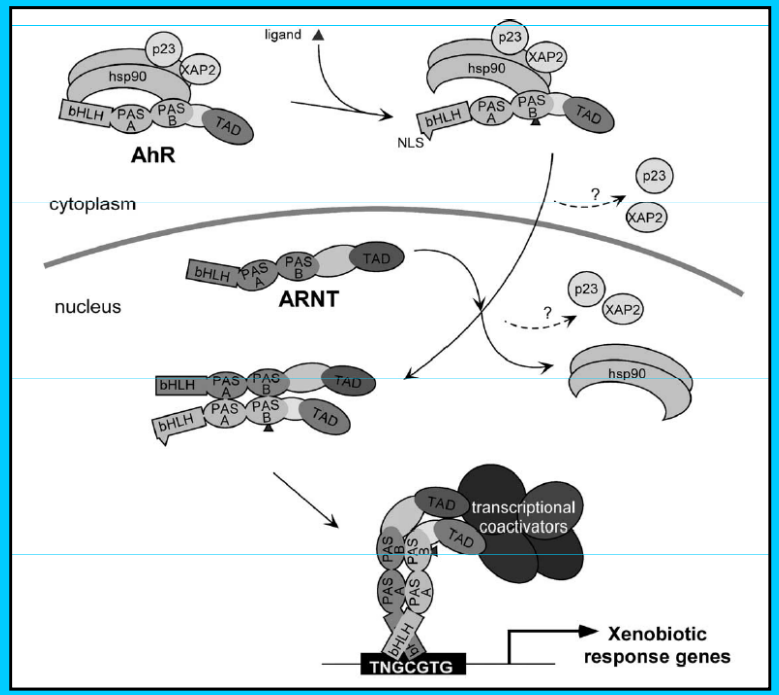


Organism:	**Name:**	**Ligand-binding:**	**Physiological function:**
Nematodes: *Caenorhabditis elegans*	AHR-1	No	Neuronal development; Behavioral effects.
Insects: *Drosophila melanogaster*	Spineless (Ss)	No	Development; Regulation of homeobox genes and dendrite morphology.
Vertebrates:	AhR (AhR1, AhR2)	Yes	Toxicity mechanisms; Liver and kidney development; Neuronal differentiation? Circadian rhytms?

Activation and effects of AhR:







„Classical" AhR-regulated genes:

contain xenobiotic response elements (XRE) or dioxin responsive elements (DRE) in their promoter region:

- **phase I and II enzymes** - ***CYP1A1, CYP1A2, CYP1B1, UDP-glucuronosyltransferase,GST-Ya, NQO1;***
- ***AhRR.***

AhR-regulated genes involved in control of cell proliferation and cell death:

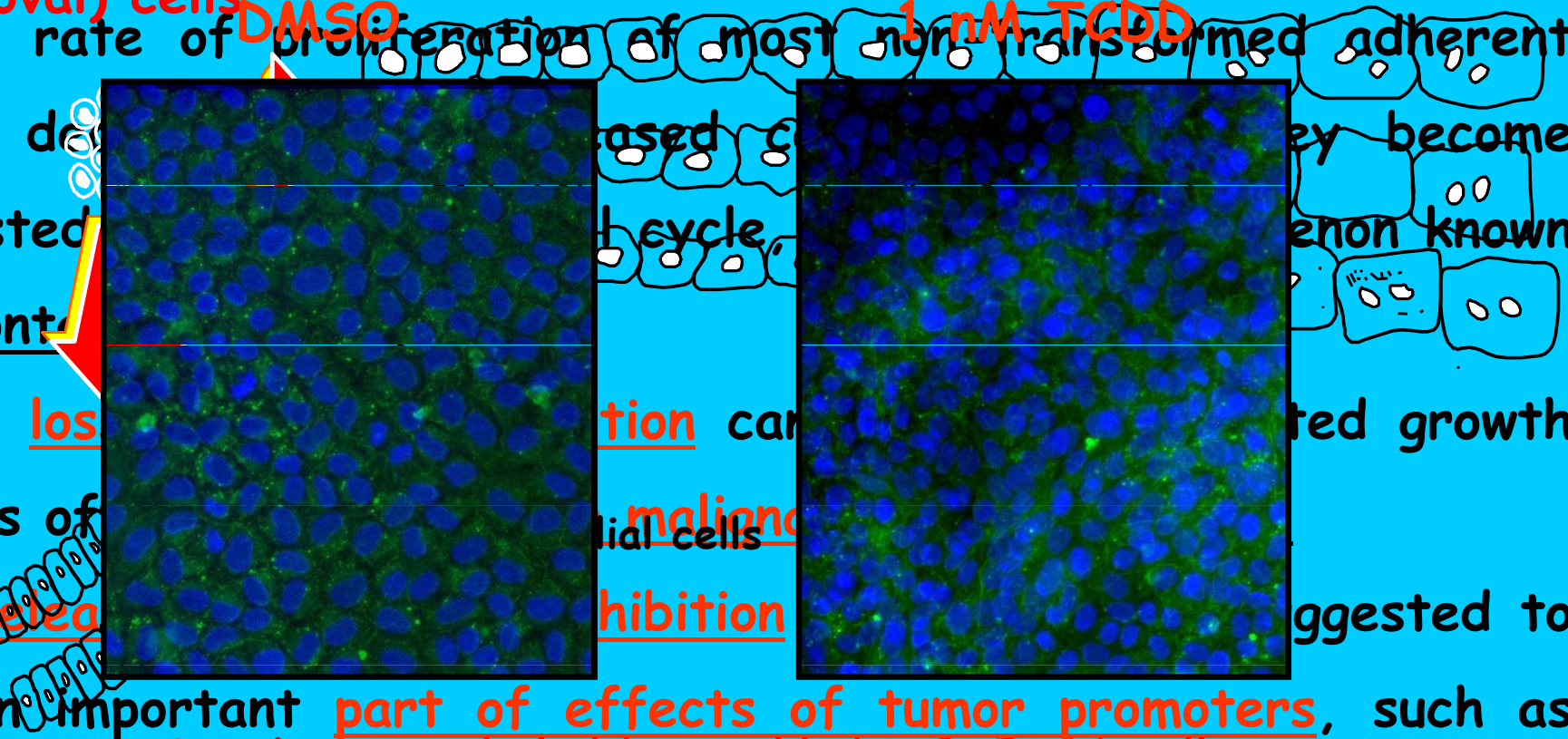
- **pro-apoptotic genes** - ***Bax;***
- **immediate - early response genes** – ***Jun, Fos;***
- **cell cycle regulation** – ***p27^{Kip1}, p21$^{Waf/Cip}$.***

Majority of cells are not actively proliferating – they are in a quiescent G0 phase of cell cycle. *In vitro* model of contact-inhibited cells.

Progenitor (oval) cells

Hepatocytes

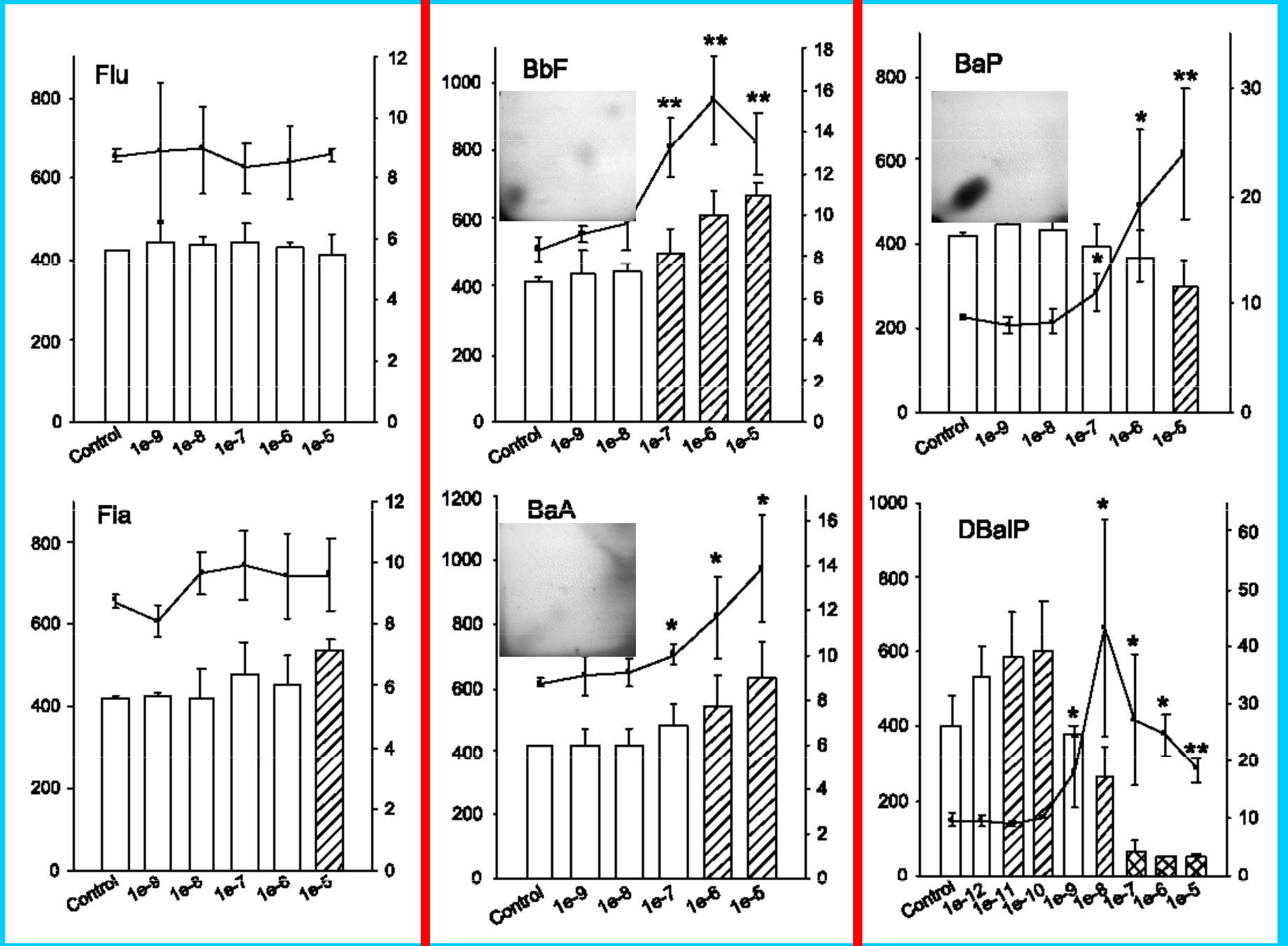
Contact inhibition:



- the rate of proliferation of most non-transformed adherent cells de… …ased c… …ey become arrested … cycle … …enon known as cont…
- the los… …tion ca… …ted growth and is of… …malianc… …lial cells
- a … …hibition … …ggested to be an important part of effects of tumor promoters, such as TPA or TCDD.

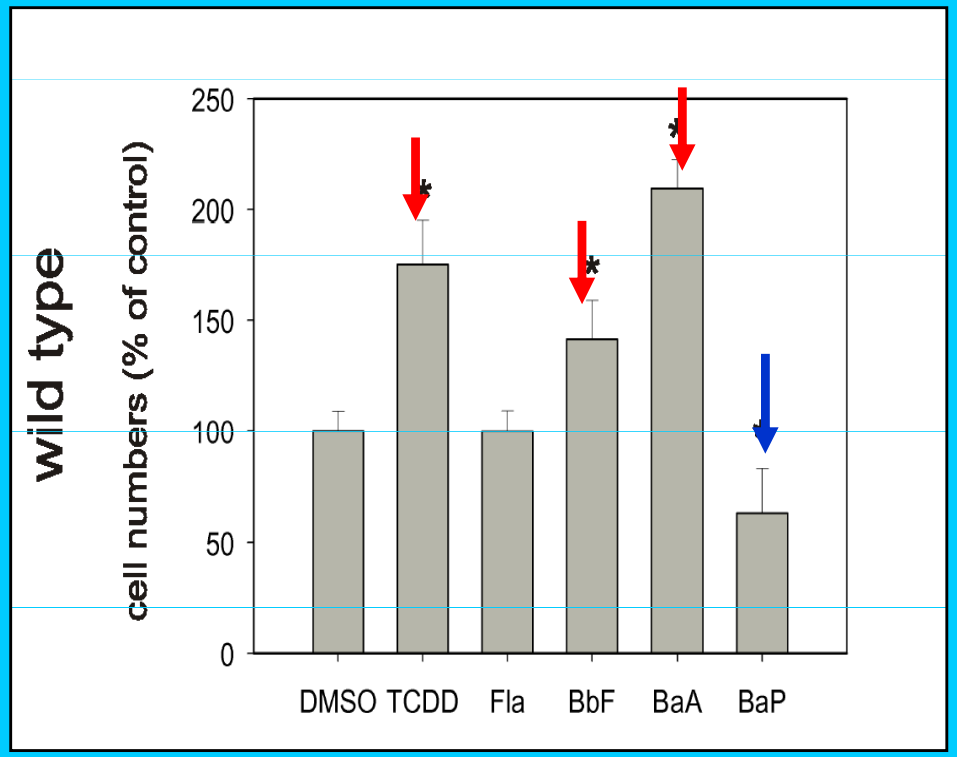
Rat liver epithelial 'stem-like' WB-F344 cells

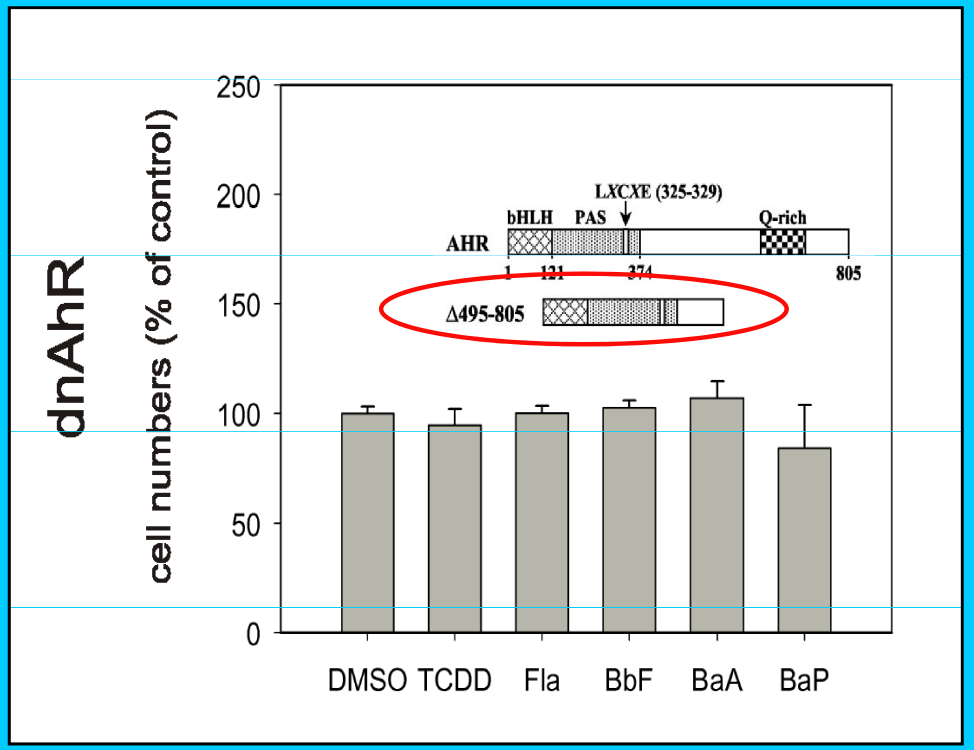
Effects of PAHs on contact-inhibited WB-F344 cells

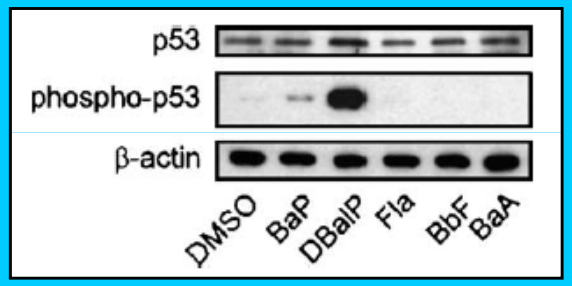


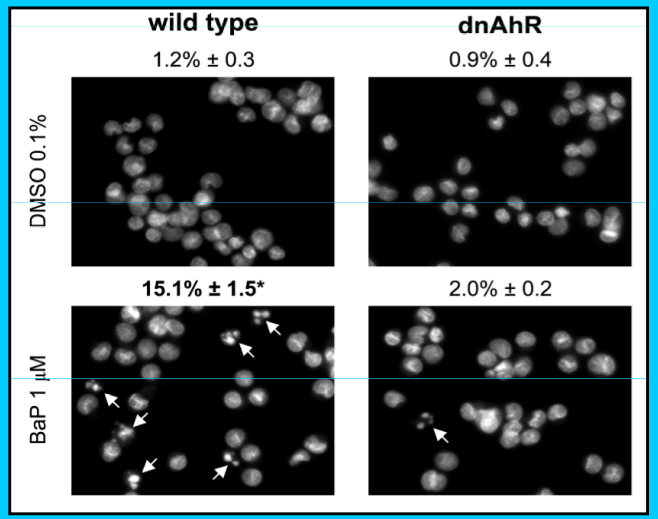
Chramostová et al., 2004

Expression of dnAhR blocks the proliferative effects of AhR ligands:



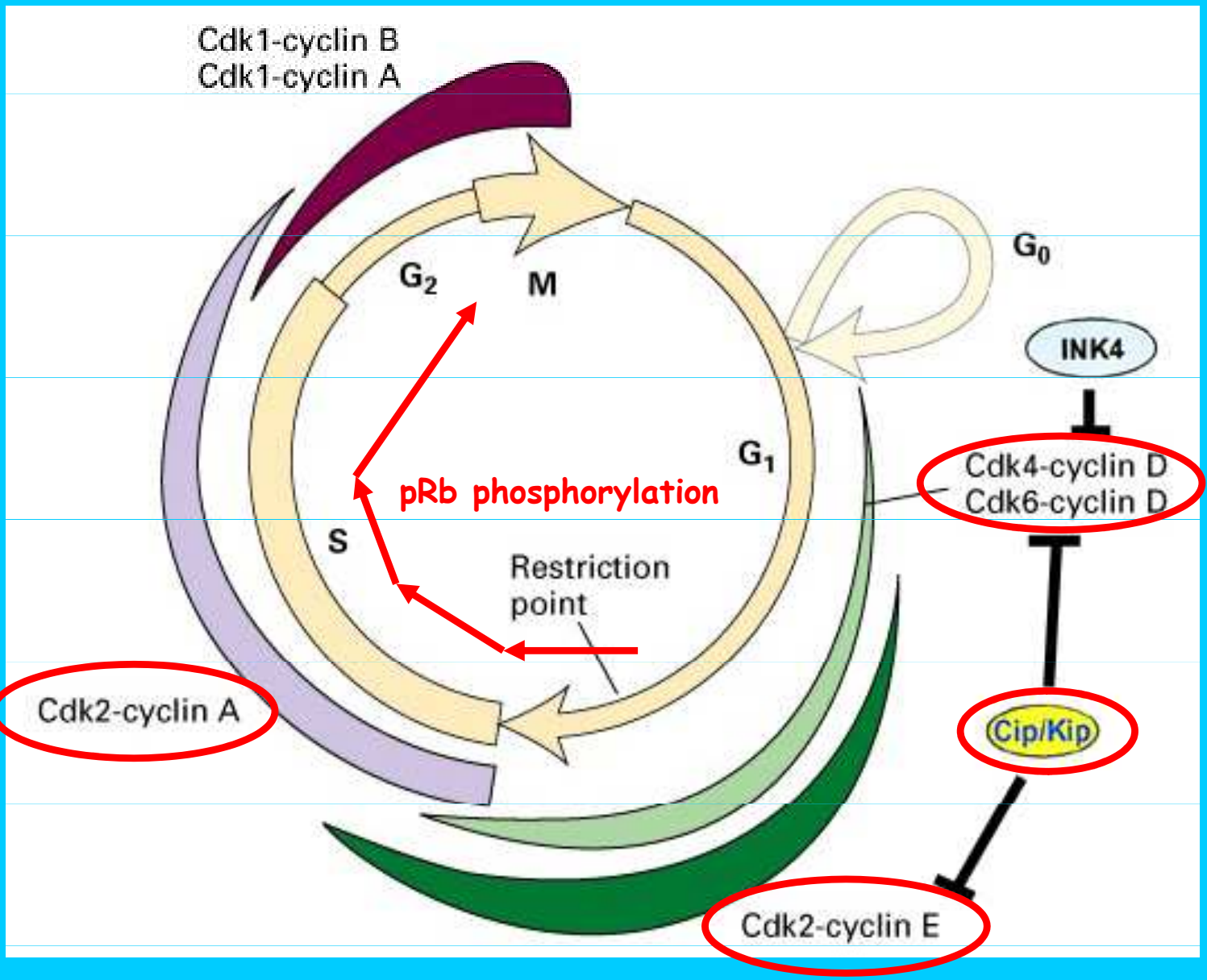




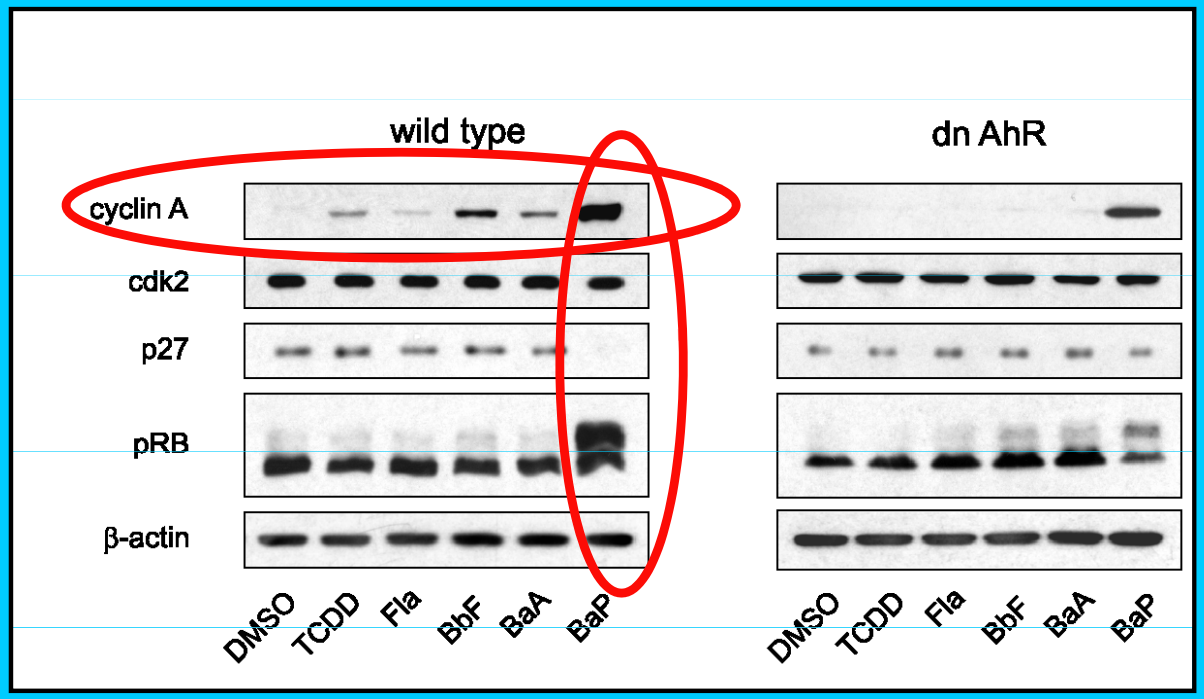


Andrysík et al., 2006
Andrysík et al., 2007

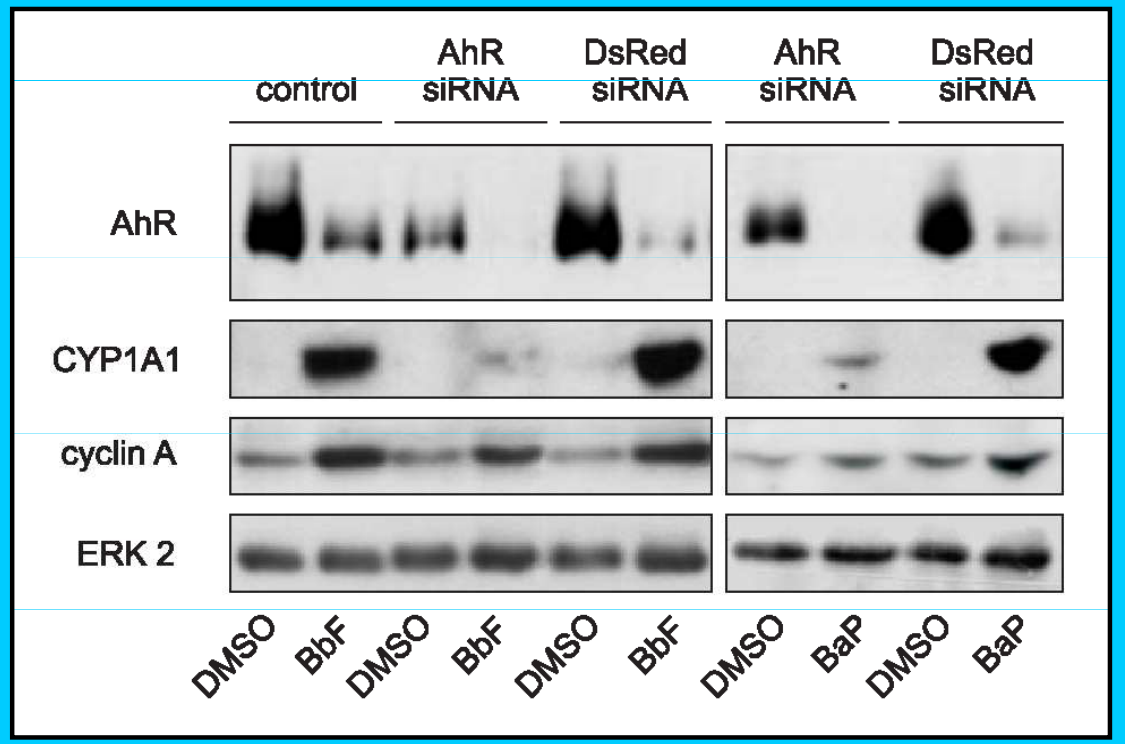
Proteins involved in control of contact inhibition:



AhR ligands modulate expression of proteins involved in G1→S cell cycle transition:

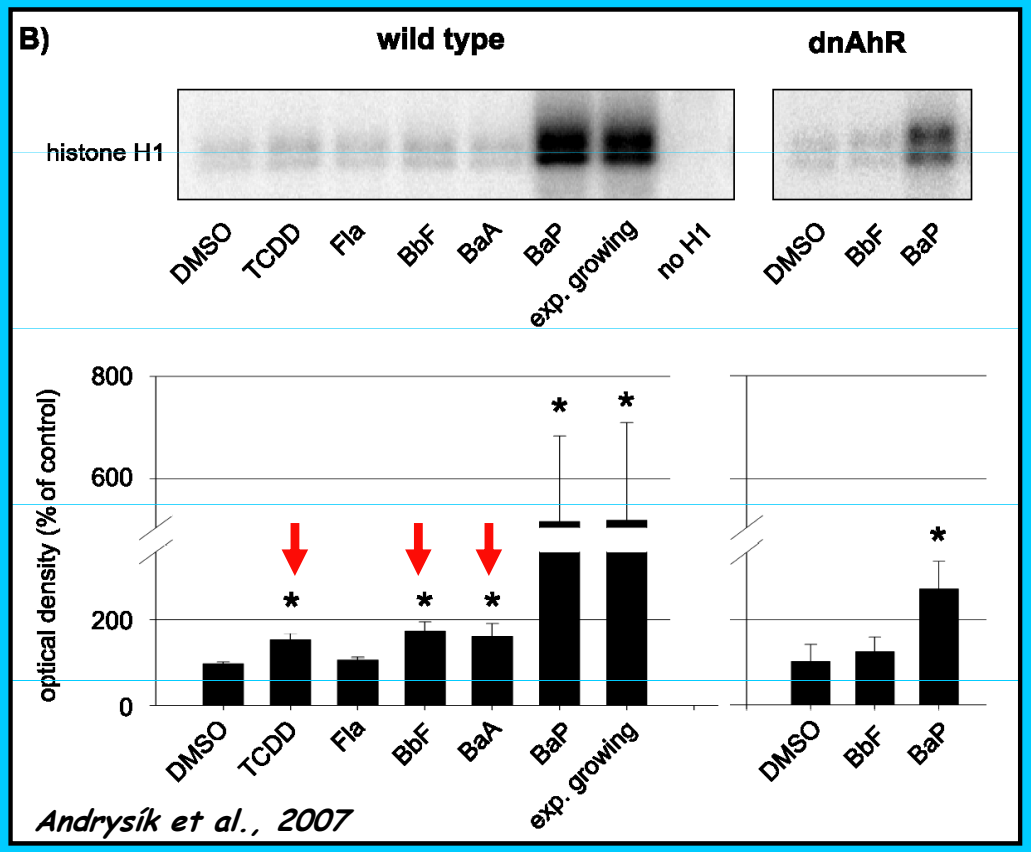


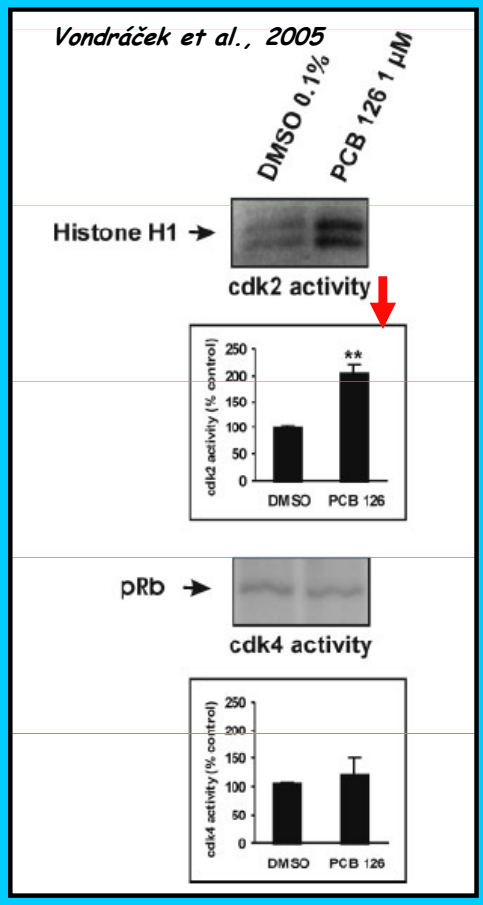
Transient knock-down of AhR blocks cyclin A induction:

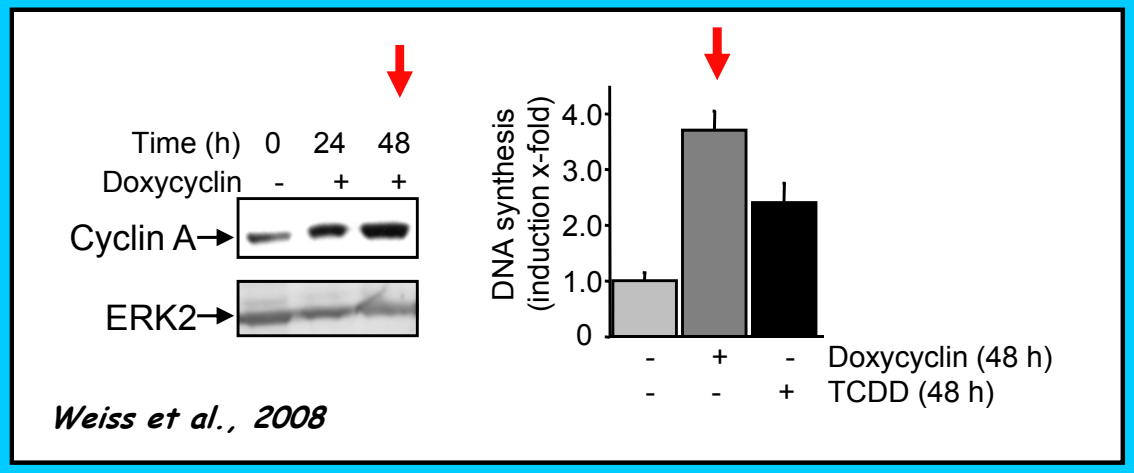


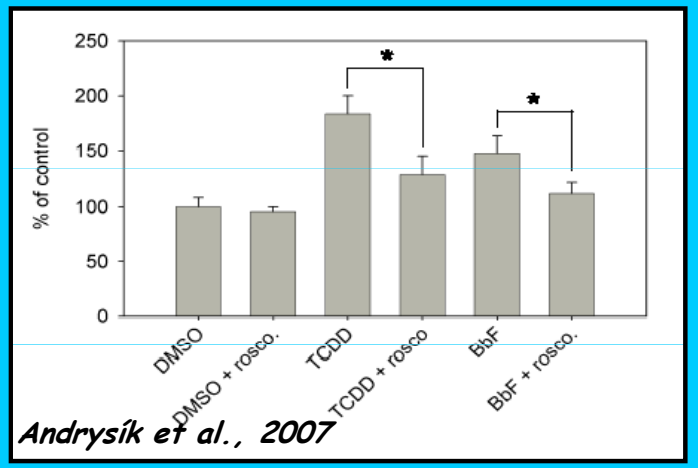
Andrysík et al., 2007

Cyclin A/cdk2 activity control is essential for the maintenance of contact inhibition:

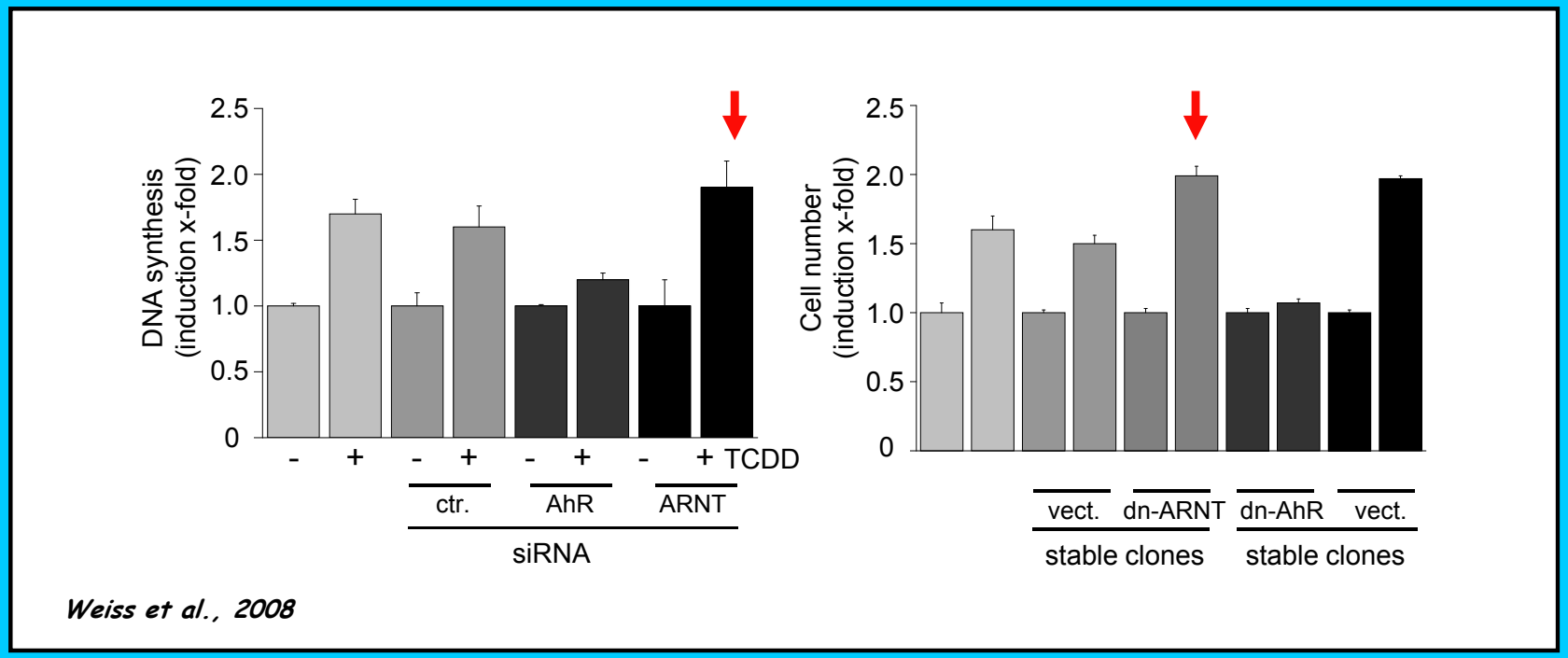




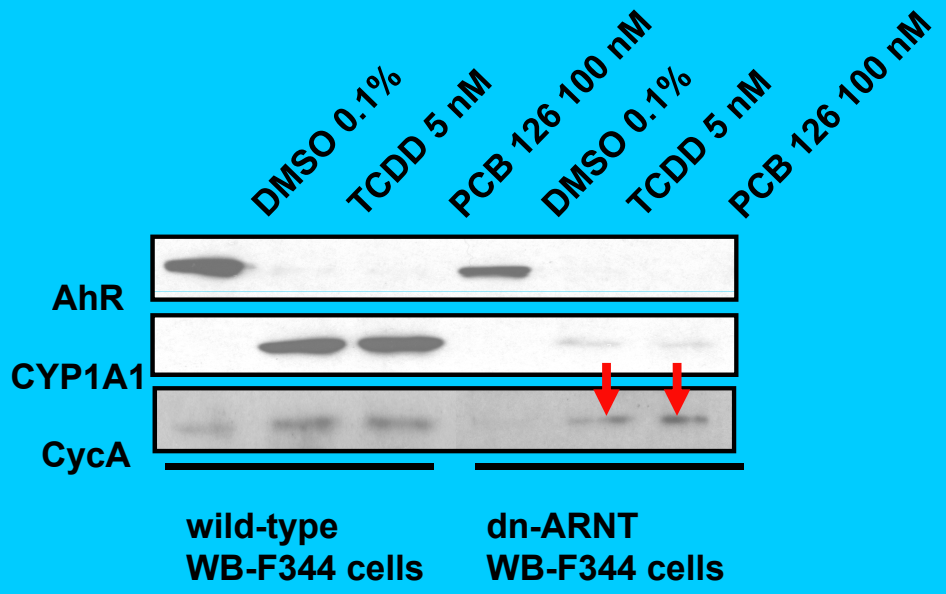


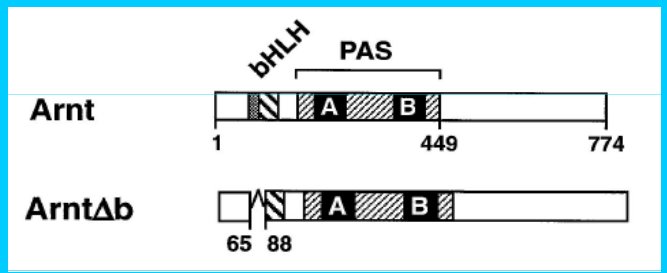


Induction of cell proliferation is independent of the dimerization partner ARNT:

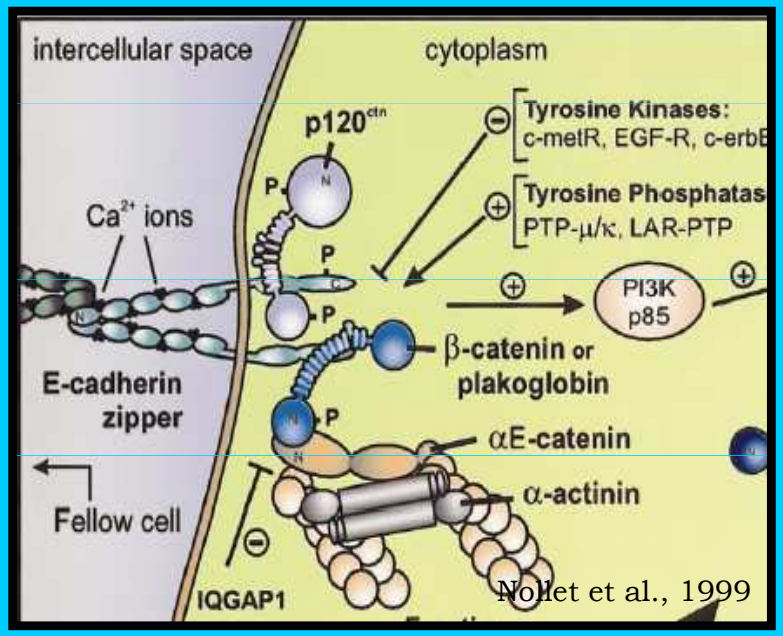


Weiss et al., 2008

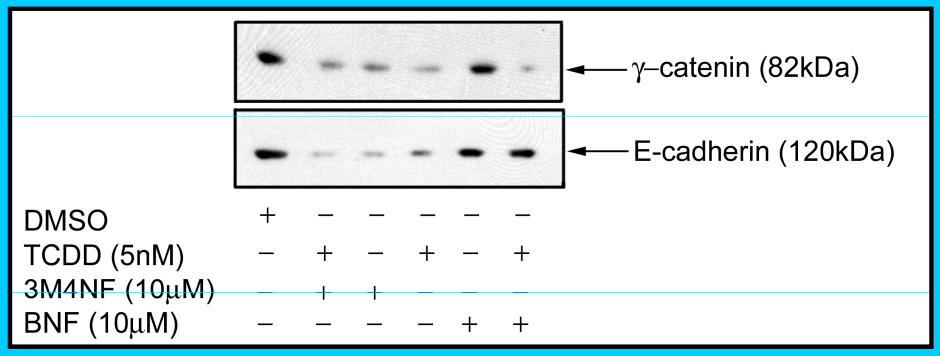


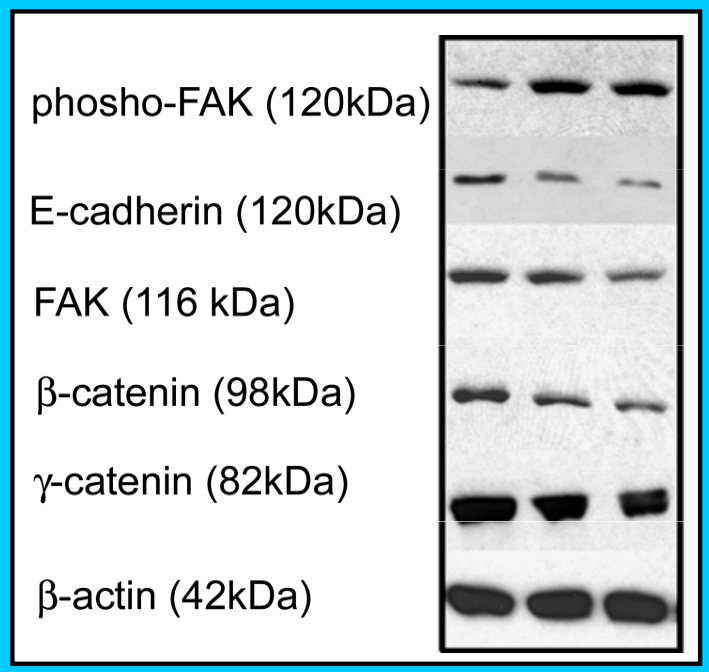


The story is more complex – AhR ligands disrupt also control of cell-to-cell communication – cell adhesion and gap junctional intercellular communication:



Nollet et al., 1999





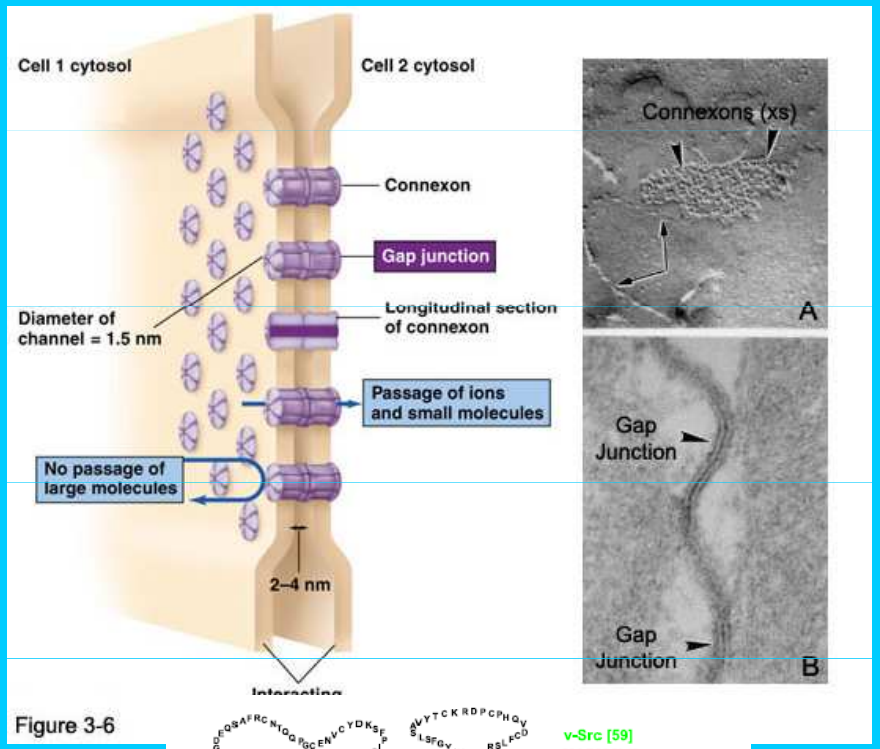
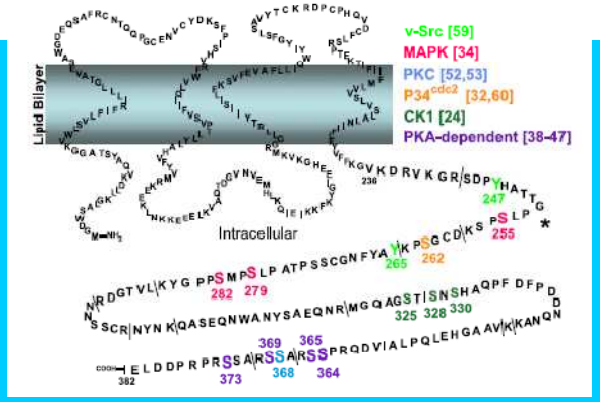
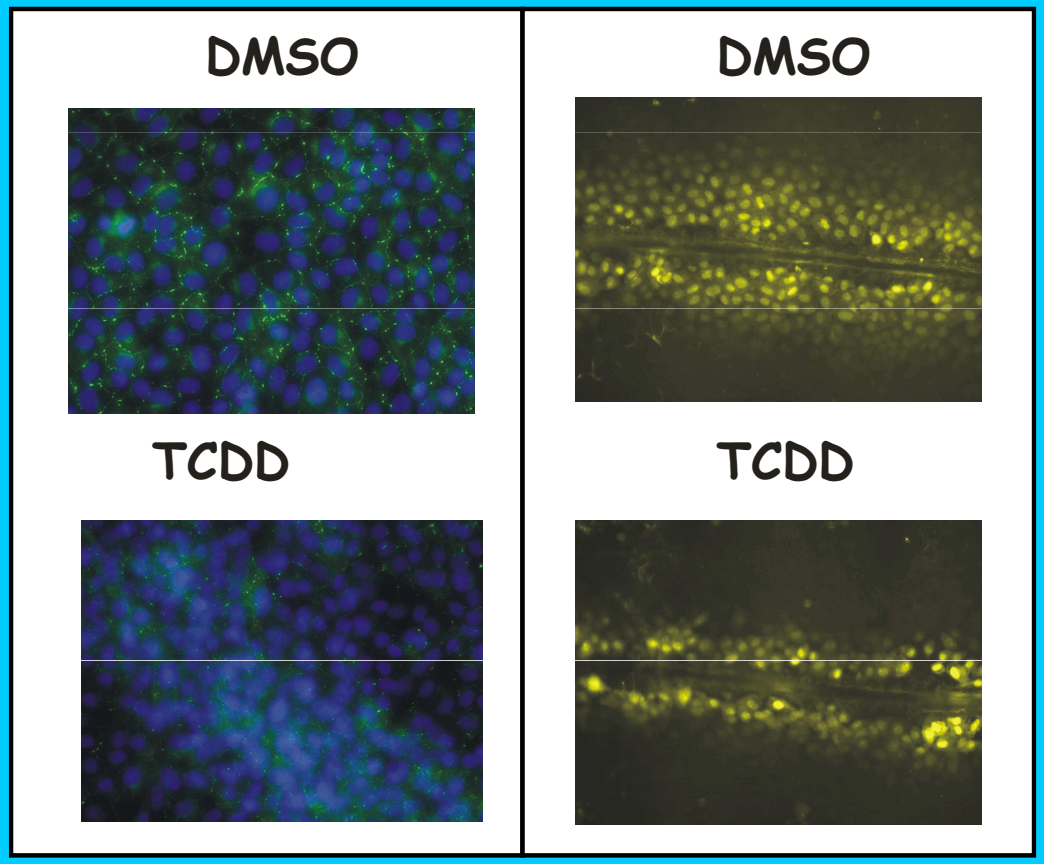
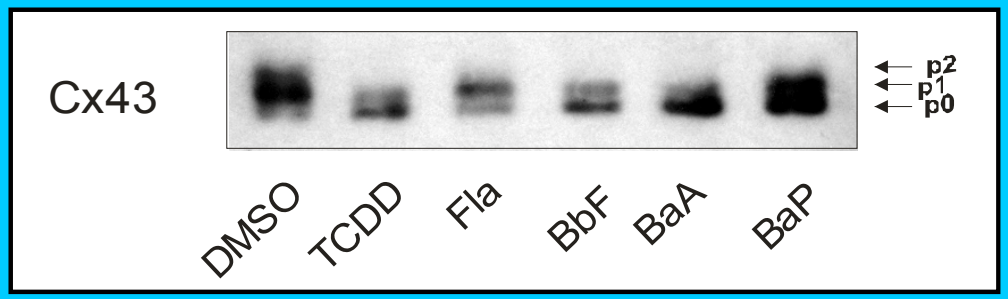
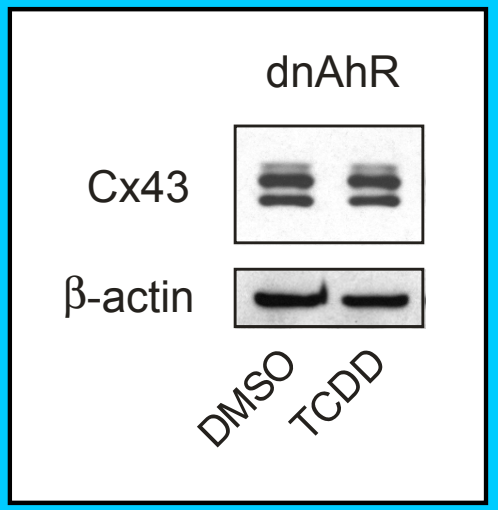

Cell 1 cytosol
Cell 2 cytosol
Connexon
Gap junction
Diameter of channel = 1.5 nm
Longitudinal section of connexon
Passage of ions and small molecules
No passage of large molecules
2–4 nm
Connexons (xs)
A
Gap Junction
Gap Junction
B

Figure 3-6

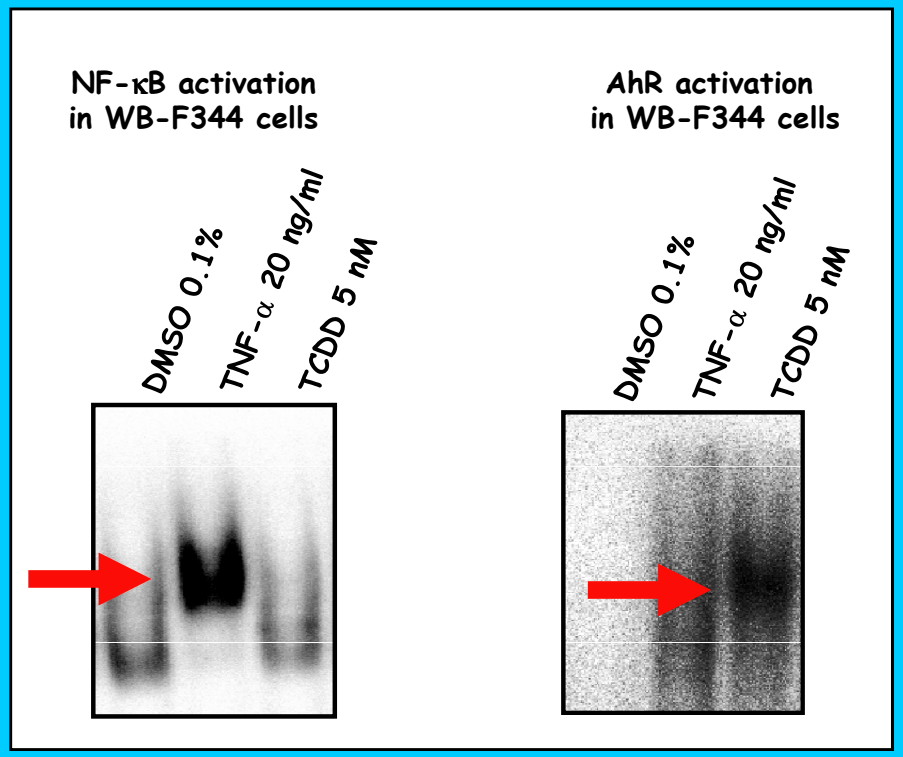

Lipid Bilayer
Intracellular
v-Src [59]
MAPK [34]
PKC [52,53]
P34cdc2 [32,60]
CK1 [24]
PKA-dependent [38-47]

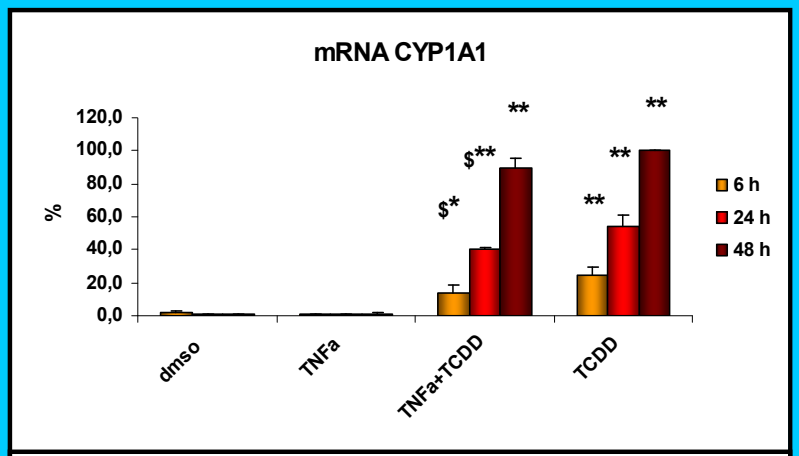

DMSO
DMSO
TCDD
TCDD

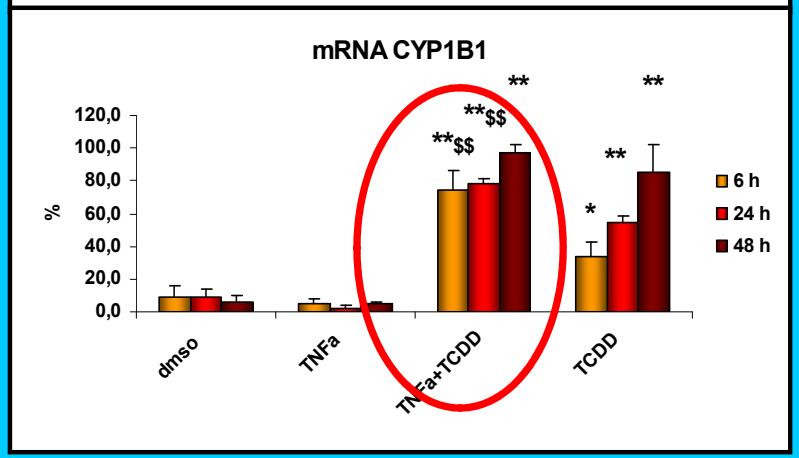

Cx43
p2
p1
p0
DMSO
TCDD
Fla
BbF
BaA
BaP

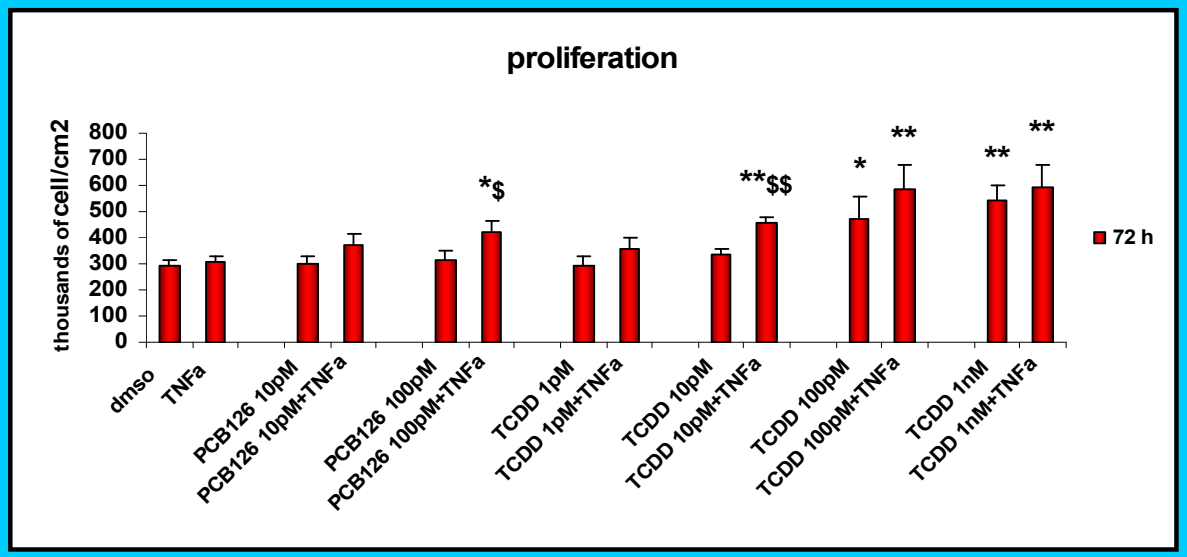

dnAhR
Cx43
β-actin
DMSO
TCDD

The complex story gets even more complex – AhR ligands interact with inflammatory and growth regulators:









Umannová et al., 2007