Fetal origins of adult disease: the fetal xenoestrogen syndrome

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REVIEW

Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement

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In this first Scientific Statement of The Endocrine Society, **we present the evidence that endocrine disruptors have effects on male and female reproduction, breast development and cancer, prostate cancer, neuroendocrinology, thyroid, metabolism and obesity, and cardiovascular endocrinology. Results from animal models, human clinical observations, and epidemiological studies converge to implicate EDCs as a significant concern to public health.**

We make a number of recommendations to increase understanding of effects of EDCs, including enhancing increased basic and clinical research, **invoking the precautionary principle, and advocating involvement of individual and scientific society stakeholders in communicating and implementing changes in public policy and awareness**. **(*Endocrine Reviews* 30: 293–342, 2009).**

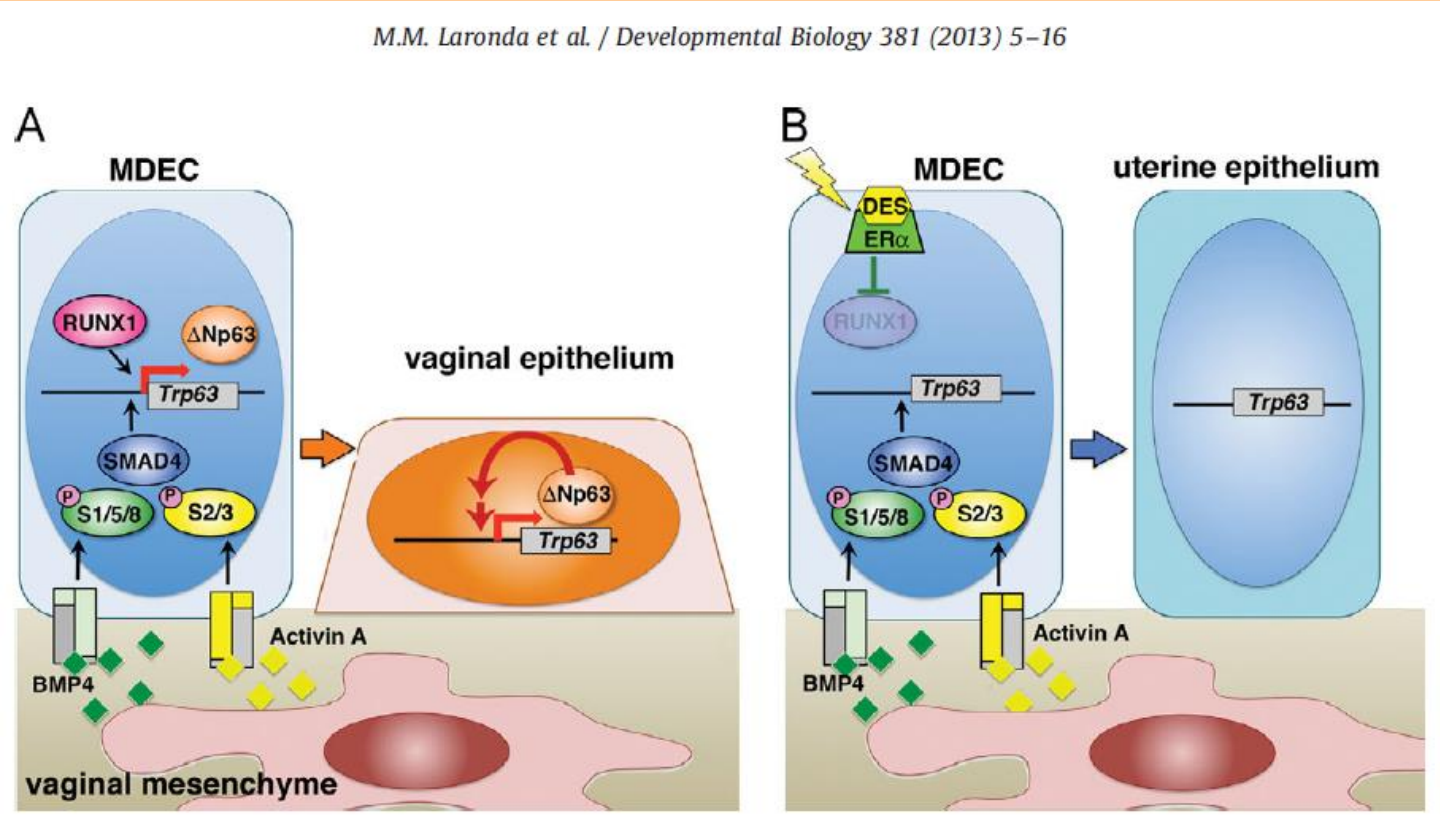
Polyphenism: one genome, many phenotypes

Araschnia levana: spring and summer morphs

DES and the fetal xenoestrogen syndrome

- This syndrome was observed in humans exposed during fetal development to the synthetic estrogen diethylstilbestrol (DES).
- DES was given to their mothers because it was (erroneously) believed to prevent miscarriage.
- Women exposed before the 13th week of gestation developed clear cell carcinoma of the vagina (1/1000), a cancer that manifested after puberty/during early adulthood.
- Additional anomalies: malformations of the oviduct and uterus, decreased reproductive success.
- Increased risk of breast cancer at the age of prevalence

DES, vaginal adenosis and clear cell carcinoma: down-regulation of RUNX 1 by DES

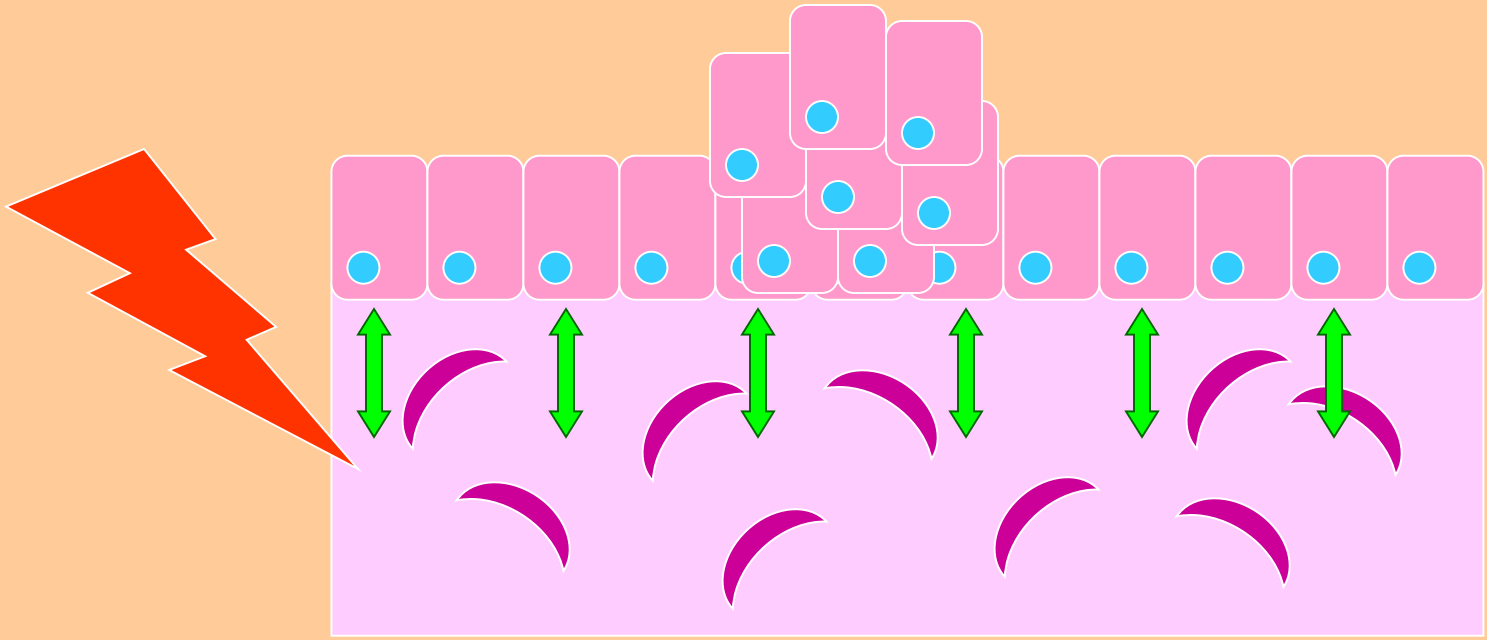


COROLARY: IT SUFFICES TO SUPPRESS OR ENHANCE THE EXPRESSION OF A PARTICULAR GENE AT A CRITICAL TIME TO PRODUCE MALFORMATIONS OR TO MAKE AN ORGAN PRONE TO CANCER DEVELOPMENT

Effects of perinatal low-dose BPA exposure: Fetal xenoestrogen syndrome

- Advanced puberty
- Altered estrous cycles and early cessation of cyclic activity
- Altered plasma LH levels, altered activation of LHRH neurons, altered LH surge
- Decreased fertility/fecundity
- Altered ovarian follicular morphogenesis
- Obesity/metabolic syndrome/altered metabolomic profile
- Altered behaviors
- Autism-like behaviors
- Increased risk of neoplastic development

The **tissue** organization field theory of carcinogenesis

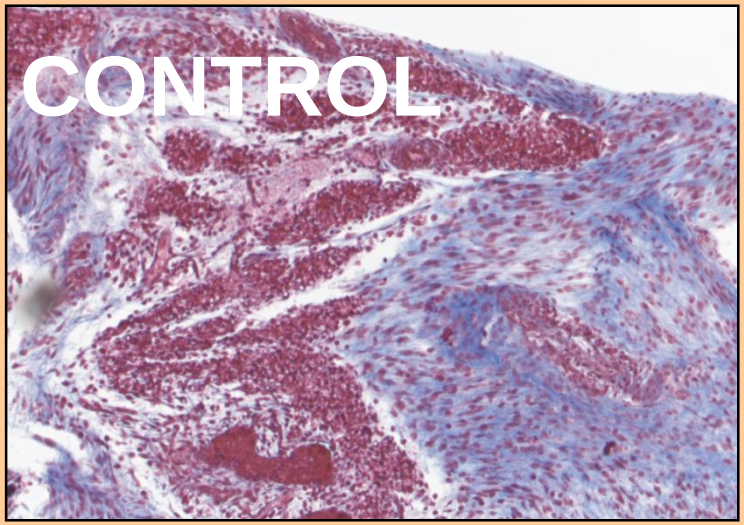


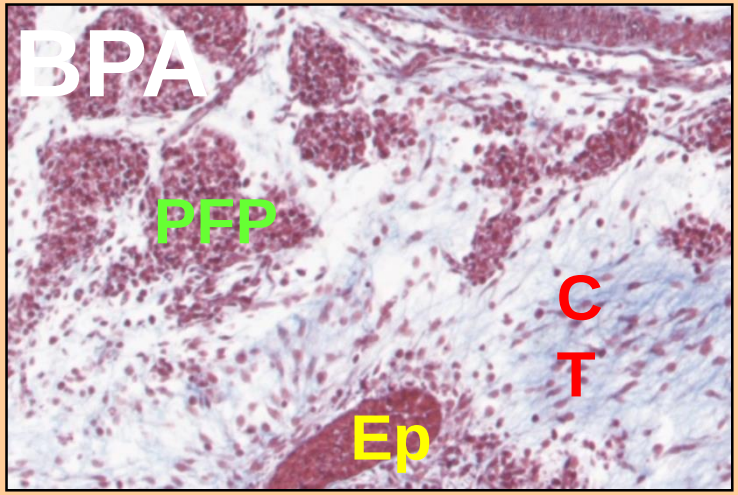
Tissue level of organization

The targets of carcinogens are ***tissues***.
Cancer is a problem of tissue organization comparable to organogenesis.

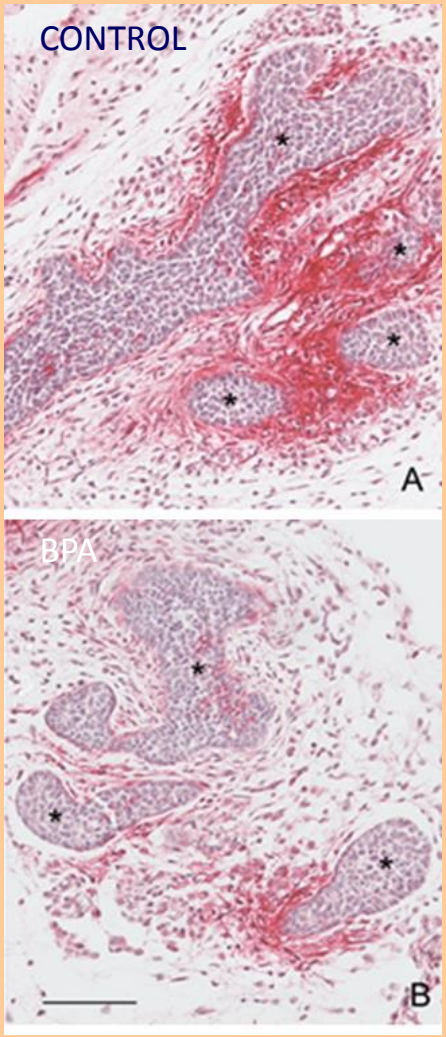
The default state of cells is ***proliferation*** and ***motility*** (consistent with evolutionary theory).

Exposure to 250 ng BPA/kg BW/day alters overall organization of the fetal MG

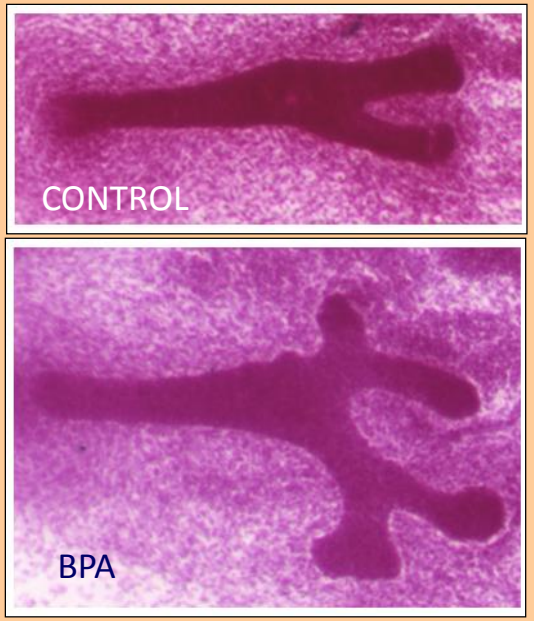


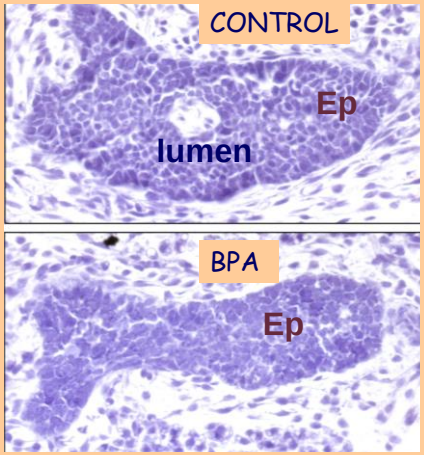


COLLAGEN

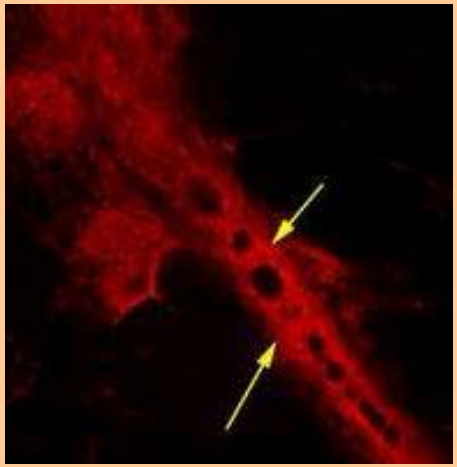


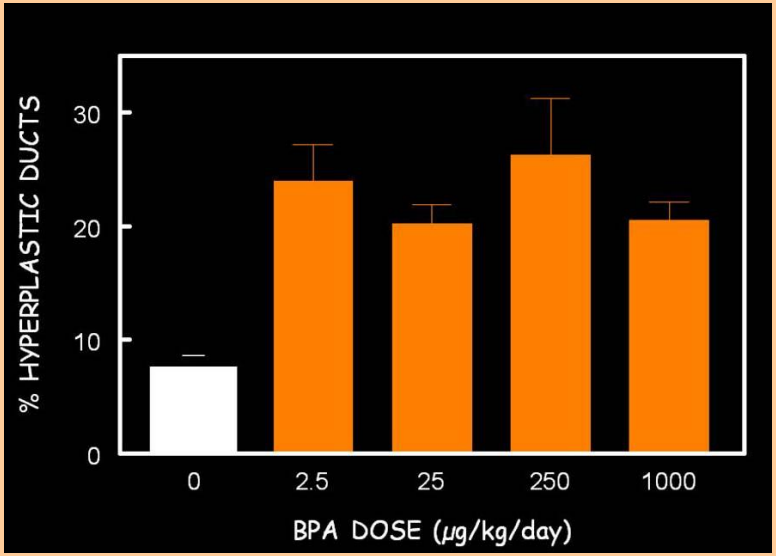
TENASCIN-C

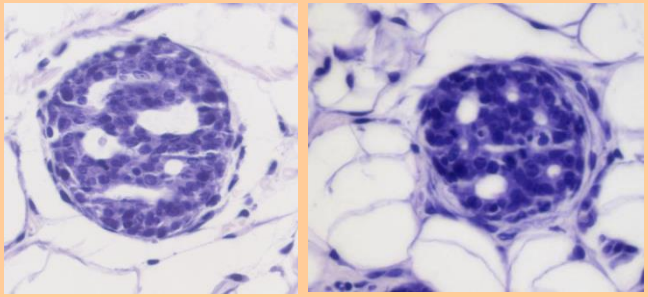


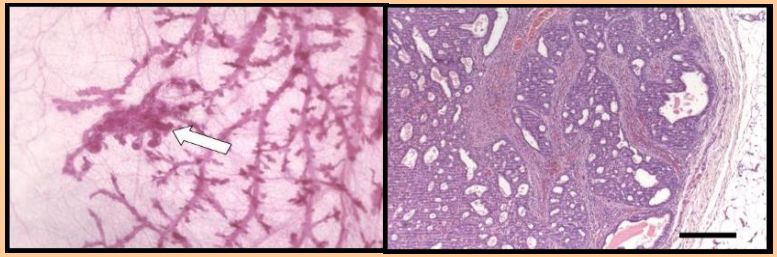


From morphogenesis to carcinogenesis:

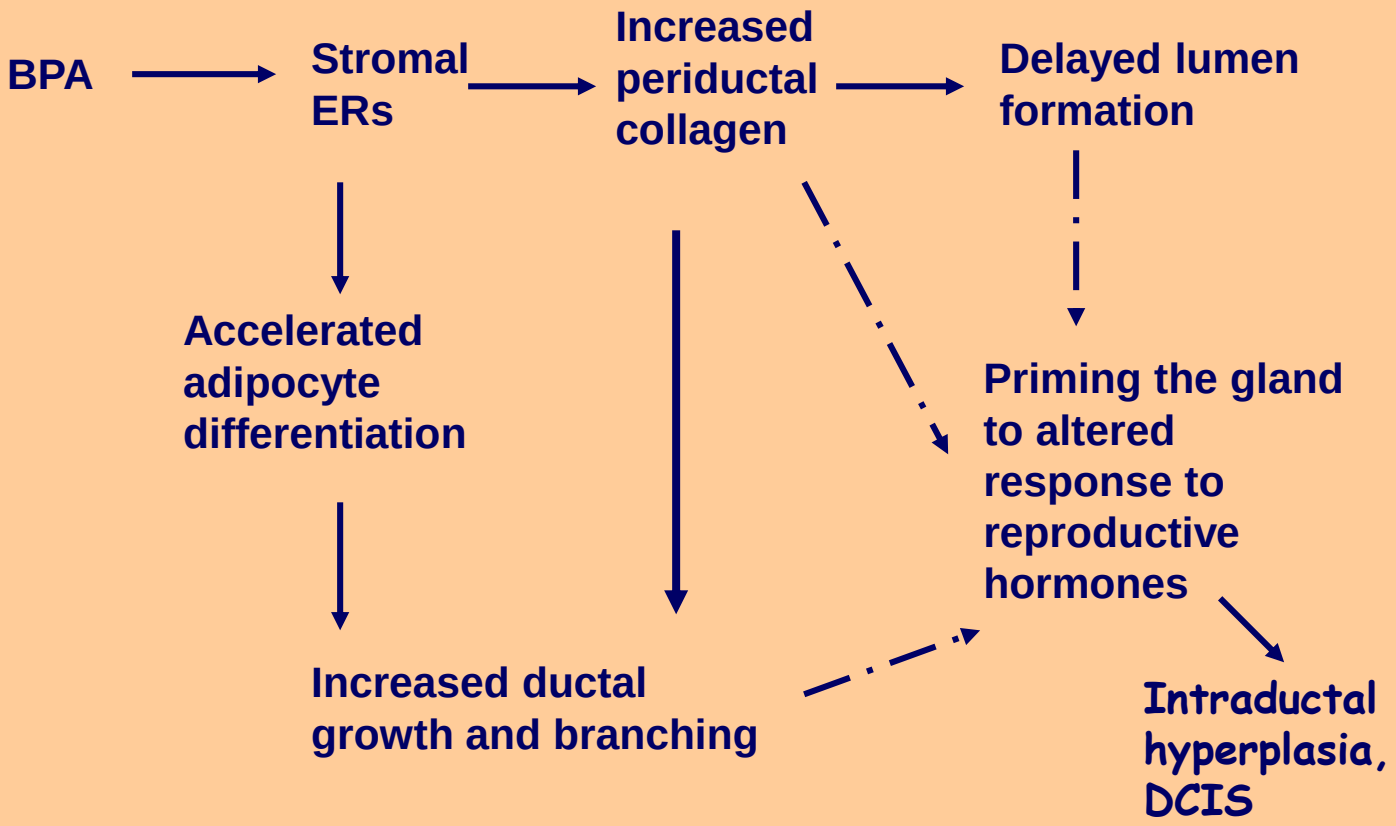








How does BPA induce neoplastic development?



BPA exposure and mammary cancer

- BPA is a complete carcinogen.
- Carcinogenic effects occur at plasma levels comparable to those found in humans and even at doses 100 fold lower in the SD rat model.
- There are multiple windows of vulnerability: fetal, neonatal, adult age.
- BPA effects on MG morphogenesis are similar in mice and non-human primates.

Recommendations regarding clinical practice

- Take a careful history of onset of reproductive disorders along with an occupational and environmental exposure history.
- Think “epidemiologically” about the patients: that is, consider possible exposure to EDCs in geographical or community subgroups showing unexpectedly high prevalence of any of the disorders possibly related to EDCs.
- Clinicians can advise patients about exposures, minimizing risks, and abiding by the precautionary principle to preserve their reproductive health and that of generations thereafter.

Diamanti-Kandarakis et al, Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. Endocrine Reviews 30: 293–342, 2009)

Recommendations regarding clinical practice

- Health care professionals need to be educated in sources and effects of environmental contaminant exposures across the life span.
- Health care professionals need to have access to straightforward and accurate health information tools to share with patients.
- Clinicians should be made aware of the potential risks posed by EDCs. This would, for instance, help them to seek evidence for exposure when treating patients presenting with early thelarche or puberty.

Diamanti-Kandarakis et al, Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. Endocrine Reviews 30: 293–342, 2009)

Soto & Sonnenschein Labs

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- **Systems Biology-Self-organization project**
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- **Oxford U.**
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- **Mass General Hospital**
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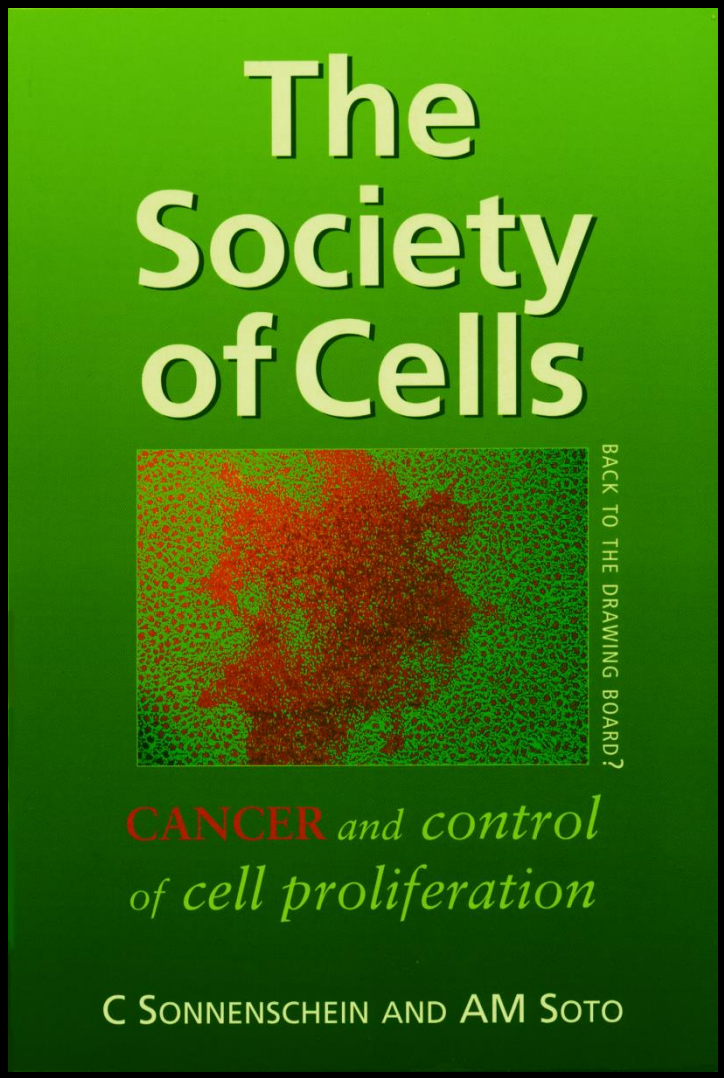

- **Theoretical biology**
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