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Letters to the Editor

Human Endogenous Retroviruses and Environmental Endocrine Disrupters: A Connection Worth Exploring?

To the Editor:

Endogenous retroviruses (ERVs) are sequences stably integrated into the genome of vertebrates and transmitted as Mendelian genes which are closely related to infectious exogenous retroviruses; it has been hypothesized that, during evolution, ERVs may have originated from ancient germ-cell infection by exogenous retroviruses (Löwer et al., '96; Urnovitz and Murphy, '96). Although most ERVs cannot be transmitted horizontally, several are actively transcribed and some can even code virus-like particles. ERV transcription can either occur spontaneously or can be modulated by a number of factors, including genotoxic and/or cytotoxic xenobiotics such as 5-azacytidine, retinoic acid, and steroids (Urnovitz and Murphy, '96; Taruscio et al., '97).

The several families of human ERVs (HERVs) overall represent up to 0.1–1% of our genome (Löwer et al., '96). Transcripts are detected in several tissues, with preferential expression in specific sites, such as the placenta (Johnson et al., '90). HERVs may contribute to genomic remodelling through reverse transcription mechanisms; specific HERVs might also constitute a reservoir of retroviral genes susceptible to activation in their respective preferential expression sites; moreover, HERVs may influence the expression of adjacent cellular genes (Löwer et al., '96). Several HERVs are consistently associated with genomic sites particularly vulnerable to physiological and environmental disturbances (Taruscio and Manuelidis, '91); it has been recently observed that HERV 4.1 maps close to several loci associated with hereditary malformation syndromes (Taruscio and Mantovani, '96).

A number of reports have suggested an involvement of aberrant HERV expression in human diseases, including germ-cell tumors (Herbst et al., '96) and pregnancy disorders such as preeclampsia (Urnovitz and Murphy, '96); however, more complete experimental and epidemiological studies are still needed to support these hypotheses.

Steroid-responsive ERVs show remarkable biological activities. The oncogenic mouse mammary tumor virus (MMTV) is highly expressed in the mouse mammary gland during pregnancy and lactation. MMTV and related ERVs possess a glucocorticoid response element; in particular, MMTV is upregulated by progesterone and glucocorticoids (Urnovitz and Murphy, '96). The human genome contains about 300 full-length sequences of MMTV-Like HERVs (HML) which include HERV-K, the most active HERV family as regards coding of viral proteins and particles (Löwer et al., '96). HERV-K is upregulated by estradiol and progesterone in vitro, and its expression is related to an increase of β-human chorionic gonadotrophin (β-HCG) (Ono et al., '87). HERV-K expression in vivo is highly and specifically increased in active seminomas and other germ-cell and trophoblast-derived tumors (Herbst et al., '96).

The single-copy ERV3 shows a highly preferential expression in steroid-regulated tissues and mostly in the syncytiotrophoblast, where it makes up a significant fraction of the total mRNA and cellular protein; in fact, products of ERV3 expression may play a role in the fusogenic and immunosuppressive properties of the syncytiotrophoblast (Larsson et al., '94; Venables et al., '95). Expression of ERV3 in the trophoblast is related to the formation of syncytium and also to increased β-HCG (Boyd et al., '93). ERV-3 is highly expressed in the fetal heart, with a peak at gestational weeks 11–17; mothers of babies affected by congenital heart block have higher levels of antibodies against ERV-3 (Li et al., '96).

Other HERVs (e.g., HERV 4.1) are preferentially expressed in the placenta; modulation by steroids is likely, although no specific information is available (Urnovitz and Murphy, '96). Moreover, although we are still far from an adequate understanding of HERV behavior during organogenesis, there are indications of phase- and tissue-specific expression of HERVs in human fetuses, possibly modulated by hormones (Mondal and Hofschneider, '82).

Presently no data exist about interactions of ERVs with environmental xenobiotics which may disrupt steroid homeostasis, the so-called "endocrine-disrupting chemicals" (EDCs) (Danish Environmental Protection Agency, '95; Kavlock et al., '96; Neubert, '97). Experimental and epidemiological data suggest that higher exposure levels to EDCs may be associated with in-

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creased risk of disorders affecting steroid-regulated tissues, such as impaired fertility or seminomas. The developing organism appears particularly susceptible to effects of EDCs, which may include malformations of the urogenital tract, and/or subtler abnormalities of differentiation, leading in turn to reduced reproductive life span or neoplasia later on. However, further information is still needed both to identify the most sensitive toxicological endpoints and to achieve a proper risk assessment (Kavlock et al., '96). In fact, the term "endocrine-disrupting chemicals" is a general one, comprising substances with different chemical structures, environmental fates, and mechanisms of actions (Danish Environmental Protection Agency, '95; Neubert, '97). Chlorinated compounds seem to exert their hormone-like or antihormone effects through receptor-mediated mechanisms; for instance, o-p'-DDT is an estrogenic agent, whereas androgen antagonism is observed for the DDT metabolite, p-p'-DDE (Kelce et al., '95), and TCDD is both antiestrogenic and antiandrogenic in laboratory rodents (Neubert, '97). Among fungicides, vinclozolin impairs male sex differentiation in rats through androgen receptor blocking (Gray et al., '94), while triazole compounds inhibit steroid synthesis (Mantovani et al., '97). Receptor-mediated estrogenic activity has been shown for compounds used in the plastic industry (e.g., phtalates) and for breakdown products of surfactants (alkylphenols) (Danish Environmental Protection Agency, '95).

It does not seem unreasonable to hypothesize that ERV expression in specific tissues may be modulated by some of the different chemicals and mechanisms of action grouped as EDCs. There is clear evidence for steroid modulation of at least two important HERVs (HERV-K and ERV3), which are preferentially expressed in steroid-regulated tissues and may have a role in human reproductive physiology or diseases. More generally, MMTV and related ERVs contain a glucocorticoid response element and, therefore, are steroid-responsive. Therefore, it is tempting to speculate that HERVs may be a target of hormone-like or antihormone chemicals. The study of potential interactions with steroid-regulated ERV families and xenobiotics might provide a better understanding of the cell- and tissue-specific effects of EDCs. More generally, the potential for HERV modulation by environmental chemicals, and its consequences, could be of interest both for basic research and for public health. In conclusion, a connection between ERVs, environmental contaminants, and steroid hormone dysfunctions might be worth exploring through both experimental and epidemiological studies.

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