Editorial

Ontogeny of Gene Expression: A Changing Environment for Malignancy

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More than 13,000 children are estimated to be newly diagnosed with cancer each year in the United States (1). Despite substantial improvements in survival over the last several decades, cancer is still the leading cause of death due to disease in children ages 1 to 14 years (2). The overall incidence rate for childhood cancer has increased significantly since the 1970s, and our recent analysis of Surveillance, Epidemiology, and End Results program data for the period 1992 to 2004 points to a continuing increase (3). As we investigate potential causes, it is important to consider what we know thus far.

Gestation is a critical window of risk for most childhood cancers. In utero initiation is supported circumstantially by the young age at diagnosis (4) as well as the histologic and cytogenetic resemblance of embryonal tumor (5) and leukemia (6, 7) cells, respectively, to those found during fetal development. Moreover, childhood cancers have been associated with congenital anomalies in several studies (8-10). Proof-of-principle has been shown by case reports of prenatal diagnosis of several cancer types (11-19) and the detection of leukemic translocations in biospecimens taken at birth (20). The well-known association of vaginal clear-cell carcinoma with prenatal diethylstilbestrol exposure extends the observation of prenatal carcinogenesis to a diagnosis made primarily during young adulthood (21).

Accumulating evidence supports in utero initiation of common adult cancers as well. Birth weight, as a broad indicator of prenatal conditions, is an accessible, widely examined datum and seems to be associated with cancer at many sites (22). Animal experiments have shown that maternal diet can modulate the risk of breast cancer in the offspring (23). Lastly, mathematical modeling of carcinogenesis confirms that gestational mutations can increase cancer risk by expanding the pool of cells susceptible to complete transformation (24, 25).

Developmental Differences in Gene Expression. Gene expression has been observed to vary widely between fetal and postnatal life, with much research seeming to concentrate on xenobiotic metabolism. Wild and Kleinjans (26) previously offered a paradigmatic example of the cytochrome P450 (CYP) phase I enzyme family. Whereas the fetal liver expresses primarily CYP3A7, CYP3A4 and CYP3A5 predominate postnatally (26-28). The expression of other phase I and phase II enzymes varies by developmental stage and tissue as well (29, 30).

Consideration of developmental differences in expression is thus critical to the successful identification of genes conferring susceptibility to childhood cancer (or any disease with in utero origins). Genes expressed exclusively or predominantly during gestation by the placenta (an organ of partly fetal origin), zygote (first 2 weeks following conception), embryo (3-8 weeks), or fetus may be preferentially selected for inclusion in candidate gene studies (see Fig. 1, derived from data in ref. 31). Developmental expression data may also provide a basis for assigning prior probabilities of association to single nucleotide polymorphisms assessed in genome-wide association studies (32), which will be especially important for childhood cancers because their rarity limits achievable sample size and opportunities for replication.

Defining the “Human Gestational Transcriptome”. Given the necessity of considering ontogeny in susceptibility gene studies, the Children’s Oncology Group Epidemiology Committee1 has adopted, as part of its research agenda, the creation of a database of genes that are mainly expressed during human prenatal development. Several approaches to defining the “human gestational transcriptome,” and their limitations, are discussed below.

The compilation of existing studies through systematic literature searches and extensive curation will be a worthwhile start. The data to be recorded should include the organ or cell population that provided tissue, the stage of gestation, and the relative level of expression. In an initial set of searches, we used the following terms:

Human + Not Mice + Not Mouse + Ontogeny + Fet* + Gene* Human + Not Mice + Not Mouse + Ontogeny + Gest* + Gene* Human + Not Mouse + Not Mouse + Ontogeny + In Utero* + Gene* Human + Not Mouse + Not Mouse + Ontogeny + Express* + Gene* where * means root searches.

1 J.A. Ross is the Chairman and L.G. Spector is a member of the Steering Committee.

(Cancer Epidemiol Biomarkers Prev 2008;17(5):1021–3)
Received 3/20/08; accepted 3/28/08.
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Copyright © 2008 American Association for Cancer Research. doi:10.1158/1055-9965.EPI-08-0275
References to expression studies in nonhuman, adult, or diseased tissues were manually screened out. As of February 2008, we have identified more than 400 citations that included 152 unique genes.

Bioinformatic inquiries may be a useful complement. Unigene is a National Center for Biotechnology Information catalogue of user-submitted expressed sequence tags grouped into gene-oriented clusters (33). In addition to breaking down the frequency of expressed sequence tags by body site and disease state, Unigene classifies seven developmental stages, including blastocyst, embryo, and fetus. Restricted expression is denoted when a stage contributes a majority of expressed sequence tags to the pool. For instance, Unigene identifies CYP3A7 (Unigene ID Hs.111944) as having expression restricted to the fetus. Comparing the results of our literature search with Unigene, we noted that 28 genes had a transcript level of at least 50 transcripts per million during the embryonic stage, whereas 44 genes had this transcript level during the fetal stage. These data will be analyzed further to determine gene function and substrates, with consideration of single nucleotide polymorphisms that may affect expression.

A common limitation to the above approaches is the inaccessibility of the developing human under normal circumstances. Many studies examining gene expression in the developing human are reticent about the source of tissue, making the extent to which reported results reflect disease states unclear. However, specimens obtained noninvasively or during frequently done intrauterine procedures hold the promise of providing information on gene expression in a large number of healthy pregnancies. Cell-free mRNA has been isolated from amniotic fluid (34) and gene expression determined from chorionic villus samples (35). Fetal cells may also be isolated from maternal blood (36); the small number of circulating cells may not be an impediment because quantifying gene expression even in a single cell is now possible (37). Cord blood and placentas are, of course, widely available and commonly scrutinized (38, 39). The expression data obtained through these approaches will be limited by a lack of tissue specificity (beyond blood and placenta) and the inability to observe periods before parturition except among pregnancies at risk for poor outcomes.

Determining tissue- and stage-specific gene expression profiles of developing animals presents no ethical constraints. Although it may be informative to examine human orthologues of genes identified from test animals, it must be kept in mind that differences in gene regulation seem to explain many of the differences in development between species (40).

Lastly, some classes of genes may be designated a priori to be expressed by the developing human; for instance, the homeobox genes that regulate morphogenesis (41). Genes that, when mutated, are embryonic lethal or produce congenital abnormalities may also be assumed relevant.

**Conclusions.** We have identified a clear need for the generation of more knowledge about gene expression during human development. Having proposed several approaches to doing so, we are confident that a sustained, collaborative effort can produce this valuable information. The proposed endeavor can be expected to greatly inform our understanding of childhood and adult cancer.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**References**


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