

than in AGA infants ($4.8 \pm 0.7 \mu\text{g/L}$ vs $3.1 \pm 0.5 \mu\text{g/L}$; $P < 0.03$). The authors concluded that the strong relation between body weight and leptin concentration at term suggests that fatty mass is a major determinant of leptin secretion in utero.

Harigaya A, et al. *J Clin Endocrinol Metab* 1997;82:3281-3284.
Koistinen HA, et al. *J Clin Endocrinol Metab* 1997;82:3328-3330.

Editor's comment: Although the physiologic role of leptin levels in utero is not completely understood, these 2 papers report new data on leptin levels at birth, their correlation with fat mass, and their postnatal decline during the first week of life.

The strong positive correlations found between serum leptin level and body weight gain in utero underscore the importance of this peptide as a marker of fetal growth. Thus, leptin could

be useful as a predictive factor of fetal outcome, although further studies need to be done to ascertain this fact. Insulin and leptin levels do not correlate significantly in Harigaya's study, suggesting different mechanisms of fetal growth modulation by these 2 growth factors in utero.

Of interest is that both groups used the same assay but did not get the same results for AGA infants. In Koistinen's paper, the figure of $14.5 \pm 2.8 \mu\text{g/L}$ was given, but in Harigaya's paper the value was $4.4 \pm 3.0 \mu\text{g/L}$. The reason for this discrepancy is not apparent.

These papers supplement the lead article on leptin by Zhang and Leibel in this issue of GGH as Zhang and Leibel did not have the opportunity to present data on intrauterine growth and leptin levels.

Fima Lifshitz, MD

Growth, Genetics, and Cancer

There is an undeniable relationship between cancer, growth, and genetics. Paraphrasing Eric R. Fearon, cancer is a genetic disease that arises from the accumulation of mutations that promote selection of clones of cells that display increasingly aggressive growth characteristics. Much of what is known about cancer genetics has come from studying hereditary cancer syndromes. Even though they collectively represent only about 1% of cancers, they have provided much insight into the pathogenetic mechanisms that give rise to cancer.

Fearon has recently examined 22 different hereditary cancer syndromes from a gene product functional perspective. Moreover, he has done this in the context of key cellular processes, such as cell proliferation, differentiation, apoptosis, and maintenance of genomic integrity. Thus, he organizes the syndromes into several functional categories. For example, several of the proteins are transmembrane receptors (proteins encoded by *MET*, *PTCH*, *RET*). Others are cytoplasmic regulatory or structural proteins (proteins encoded by *NF1*, *PTEN*, *APC*, *NF2*), transcription factors or regulators (proteins encoded by *p53*, *WT1*, *RB1*, *VHL*), or cell cycle regulators (proteins encoded by *CDK4*, *p16*). Finally, many proteins are involved in repair of DNA damage (proteins encoded by *MSH2*, *MLH1*, *PMS2*, *ATM*, *BRCA1*, *BRCA2*, *FACC*, *FACA*, *XPA*, *XPB*, *XPD*, *BLM*).

Several interesting observations come from this analysis. For instance, when genetic heterogeneity has been found, ie, hereditary nonpolyposis colorectal cancer, inherited melanoma, and familial breast cancer, all of the implicated genes function in a conserved pathway. For example, *MSH2*, *MLH1*, and *PMS2* in patients with hereditary nonpolyposis colorectal cancer adversely affect DNA mismatch recognition and repair.

One of the puzzling observations is that cancers are limited to certain tissues in most syndromes, yet the genes are widely expressed. It is suggested that many of the implicated genes

function in interesting or overlapping pathways that branch and converge differently in different cell types. Another explanation is that genes simply may have different functions in different cell types. Fearon emphasizes that other factors, such as other genes, diet, environment, and lifestyle, substantially affect the expression of cancer in mutation carriers.

Fearon ER. *Science* 1997;278:1043-1050.

Editor's comment: This excellent review puts a different slant on hereditary cancer syndromes. It not only organizes information from 10 years of literature concerning cancer syndromes but also presents the material in a functional context that allows one to create a big picture of how the syndromes relate to one another and to normal biologic processes.

William A. Horton, MD

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