

leads to proteolytic cleavage of IGF-1 and loss of its protective binding of IGF-1. The authors conclude that a minimum concentration of IGF-1 in the serum, higher than what they observed in the double gene-deletion mice, is necessary for normal bone and somatic growth.

Following administration of IGF-1 by injection, the animals with the double gene deletion experienced increased serum IGF and IGF-1 concentrations accompanied by restoration of normal bone growth and modeling, as well as increased somatic growth. These findings are consistent with their observation that the restoration of normal growth can be accounted for by increased serum IGF-1 concentrations above the minimal levels necessary for normal growth to occur.

This paper provides confirmatory evidence that hepatic derived IGF-1 and acid labile subunit are not necessary for normal growth provided minimal serum levels are maintained from non-hepatic sources including autocrine/paracrine production by target tissues.

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References

1. Yakar S, et al. *Proc Natl Acad Sci USA* 1999;96:7324-9.
2. Daughaday WH, et al. *Nature* 1972;235:107.

The BRCA2 Gene's Role in Fanconi Anemia and Various Cancers

Fanconi anemia (FA) is an autosomal recessive disorder in which affected subjects have great susceptibility to neoplasia early in life, including acute myeloid leukemia and squamous cell carcinoma. Bone marrow failure is also frequent, as well as mutations in at least 8 groups of FA patients (A, B, C, D₁, D₂, E, F and G) and germline mutations in six of these have been identified in 6 genes (A, C, D₂, E, F and G). The FA cells manifest many broken and misshapen chromosomes reflecting that FA proteins participate in the repair of DNA damage, either stimulating or inhibiting normal repairs. Five of the 6 genes previously described combine in a multi-subunit nuclear complex which activates by ubiquitination of the protein product of a sixth gene (FANCD2) which is involved in the process of DNA repair. Howlett et al¹ identified a 7th gene by demonstrating that homozygous "loss of function" mutations occurring in the BRCA2 gene (causing breast cancer as does the BRCA1 gene) occurs in a subset of patients with FA.

Witt and Ashworth² stated in the introduction of their commentary; "Important discoveries are so neat and satisfying that, in retrospect, they seem obvious. Howlett et al disclosed that the inheritance of two defective copies of the BRCA2 breast cancer susceptibility gene can lead to FA. The BRCA2 protein is thought to be important in the repair of DNA damage. Cells lacking BRCA2 inaccurately repair damaged DNA leading to gene mutation and progression of tumors and are particularly sensitive to DNA cross-linking agents. Howlett et al demonstrated that one of the previously unidentified FA genes (FANCD1) is BRCA2." No BRCA1 mutations were found in the patients studied by Howlett et al. However, all the authors of all three papers speculatively agreed that the 6 previously cloned genes are linked in a common pathway with BRCA1 and BRCA2 genes.¹⁻³

Venkitaraman³ in his closing comments stated; "The network which connects BRCA and FA proteins in DNA

repair includes at least two other molecules - ATM (mutated in ataxia telangiectasia) and CHEK2 - whose inactivation is also associated with carcinogenesis in several tissues. Although the precise functional connections between the molecules in this network remain obscure, it is clear we are glimpsing an important tumour suppressor pathway whose disruption may underlie many different types of human cancer."

1. Howlett NG, et al. *Science* 2002;297:606-609.
2. Witt E, Ashworth A. *Science* 2002;297:534.
3. Venkitaraman AR. *Lancet* 2002;369:1343-1345.

First Editor's Comment: *Heterozygous inactivating germline mutations in BRCA1 and BRCA2 have been linked to increased susceptibility to breast and ovarian cancer in women.¹ In the tumors that develop in these patients, there is loss of heterozygosity of BRCA1 or BRCA2. Both BRCA1 and BRCA2 are important for repair of DNA damaged by exposure to ionizing radiation and cross-linking, and do so by interrupting the cell cycle while promoting repair of the damaged DNA strands.¹⁻³ The carboxyl-terminal domain of BRCA2 likely binds to single strands of DNA at the site(s) of a double stranded DNA break and facilitates the binding of other repair factors such as RAD51, an important member of this family. This article is of interest because it demonstrates the difference in phenotypes that result from heterozygous as compared to homozygous germline mutations in BRCA2. How this mutation affects somatic growth and the reproductive endocrine system is unclear. However, Wajnrajch et al⁴ found aberrations of endocrine function in 44/54 primarily prepubertal patients with FA.⁴ Abnormalities included short stature with mean height SDS -2.35 (due to growth hormone insufficiency in 44%), hypothyroidism (36%), hyperinsulinemia (72%), impaired glucose tolerance (25%), and diabetes mellitus (2%). Skeletal maturation*

was approximately one year delayed behind chronologic age; predicted adult height in 22 subjects was -1.24 SDS.

References

1. Wilson JH, Elledge SJ. *Science* 2002;297:1822-1823.
2. Yang H, et al. *Science* 2002;297:1837-1848.
3. Witt E, Ashworth A. *Science* 2002;297:534.
4. Wajnrajch MP, et al. *Pediatrics* 2001;107:744-754.

Second Editor's Comment: The phenomena described in the papers given as references are phenomenal. The first 3 references read as a package will permit any reader not informed about such matters to advance into the upper elementary levels, both in respect to understanding the physiology and pathophysiology of Fanconi Anemia, breast cancer, and to the interactions of genes and gene products.

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Serum Zinc in Infants and Preschool Children in the Jeddah Area: Effect of Diet and Diarrhea in Relation to Growth

Dr. Bahijri has written a thoughtful analysis of the etiology and effect of zinc deficiency on wasting and stunting of 728 children in 5 age groups (4-6, 6-<12, 12-<24, 24-<36, and 36-72 months). Using the concept of weight for height, the subjects were classified according to their grade of wasting, and using the concept of height for age, the subjects were classified according to their grade of stunting. The dietary, auxological, and chemical evaluations were carefully done in accord with the most modern standards and techniques. The study was undertaken to determine the prevalence of zinc deficiency in the Jeddah (Saudi Arabia) area among preschool age children, to see whether such a deficiency is a cause of retarded growth, to determine whether a relationship exists between height for age and serum zinc concentrations, and if possible to determine the causes of zinc deficiency.

The authors presented serum zinc levels in the various age groups for subjects: (1) without stunting and wasting, (2) with various grades of wasting, (3) with various grades of stunting, and (4) with both stunting and wasting. Many subjects in each group had zinc levels <10.4 $\mu\text{mol/L}$ which is frequently cited in the literature as the cut off for normalcy. However, the lowest mean serum zinc levels were found in the patients in the group with stunting and wasting. Whereas those who had neither stunting nor wasting had the highest levels. The older stunted children (group 3) had lower zinc levels than those found in the younger children. All patients with wasting (group 2) had hypozincemia.

The authors concluded that diarrhea rather than low dietary intake mostly accounts for the low zinc levels in infants (4-12 months). As the subjects passed the 24 month mark, diet deficiency became the presumed major cause of hypozincemia and this cause became more dominant as the etiology in the oldest age group (36-72 months).

The importance of zinc in biology is well reviewed, including that zinc is known to influence cell division, growth and development, as well as sexual maturation. It is needed also as a membrane stabilizer, and is

essential for the integrity of the immune system. More than 100 enzymes require zinc as a cofactor, and zinc seems to be involved in the proper storage and release of insulin, growth and repair of tissues, wound healing, ability to taste food, production of prostaglandins, mineralization of bone, blood clotting, function of vitamin A, and functions of the thyroid hormones.

Not commonly known, an important predisposing factor for zinc deficiency is the extensive use of cereal protein which limits the availability of zinc due to high phosphate and phytate content. The recommended dietary allowance of the Food and Nutrition Board and the National Academy of Sciences in the United States is 15 mg/day for adult males and 12 mg/day for adult females, with higher recommended levels during pregnancy and lactation. Requirements for infants and children are relatively high in relation to body size because of increased requirements for physical growth.

The best sources for zinc in the diet are meat and fish; the bioavailability of zinc from animal products is considered to be greater than that from plants. Diarrhea is associated with zinc deficiency and low serum zinc concentration. Suggestions have been made that growth retardation commonly seen in children in developing countries is related to zinc nutritional deficiency.

Unfortunately, it was not feasible to interpret the direct effect of zinc deficiency on wasting or stunting although a significant majority of subjects with wasting and/or stunting had severe deficiency. The author summarized: "The result of this work shows a high incidence of low serum zinc levels among Jeddah-area infants and young preschool children, which is associated with diarrhea and wasting in the first two years of life, and generally low dietary intake, wasting and/or stunting in older children. Zinc supplementation is recommended for certain categories of subjects to improve appetite and hence dietary intake, immunocompetence, and anthropometric measurements."

Bahijri SM. *Annals of Saudi Medicine* 2002;21:324-329.