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Increased superoxide dismutase and Down's syndrome

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Summary The enzyme superoxide dismutase (SOD) is a constitutive enzyme coded by a gene located in Chromosome 21 (21q22.1). Thus, the tissues from patients with trisomy 21 contain 50% more SOD activity. It is often suggested that the increased SOD content in the cells of Down's syndrome patients is responsible for many of the neurological symptoms of this disease. This hypothesis is not supported by most of the available data. In this paper we discuss why the increased SOD activity should not influence neuronal function and propose, instead, that the main problem may be an overexpression of other genes also located in chromosome 21 such as the beta amyloid precursor, as well as oncogenes and other Down's syndrome-related genes. We also propose that the increased SOD may be, instead, responsible for the increased incidence of Down's syndrome in children of older women. The augmented antioxidant protection resulting from an extra copy of chromosome 21 may, with time, selectively protect human oocytes from apoptosis, increasing their proportion with age, explaining the higher incidence of this disease.

Down's syndrome is a genetic disease characterized by a variety of symptoms, including mental retardation, increased neuronal apoptosis, early aging, etc. Several groups proposed that many of the neurological symptoms of Down's syndrome patients result from the increased intracellular activity of CuZn superoxide dismutase (SOD), an enzyme coded by chromosome 21 (21q22.1) which converts superoxide anion into H_2O_2 (1–3). Since this is a constitutive enzyme, its activity is increased by 50% in patients with trisomy 21. Thus, supporters of this hypothesis assume that this increase in SOD causes an imbalance in the steady state oxidative stress, increasing H_2O_2 formation, which in turn increases the steady state formation of other oxidants such as hydroxyl radical.

This hypothesis has never been unequivocally tested, and most of the available evidence does not support it. For example, transgenic mice designed to overexpress SOD show minor abnormalities in the tongue neuromuscular junctions, but they do not share the main characteristics of Down's syndrome such as increased apoptosis or neuronal degeneration (4,5). Moreover, the same mice turned out to be more resistant than control mice to oxygen toxicity (*6*). Therefore, since oxygen toxicity is a result of an overproduction of reactive oxygen species, the protection by SOD indicates that overexpression of this enzyme cannot cause oxidative stress. Another study has shown that SOD overexpression increases survival of transplanted neurons (*7*).

More specific studies have also shown that there is not always a correlation between SOD expression and mental retardation or increased brain damage. For example, some Down's syndrome patients have normal SOD activity (*8*). Even when looking at SOD content in species that are phylogenetically related, one finds that while man and chimpanzees express similar amounts of SOD, orangutans have twice as much activity (*9*). On the other hand, thymus cells from mice trisomic for chromosome 16 (which contains the gene for SOD) appear to show increased apoptosis (10), which was attributed to an increased formation of hydrogen peroxide. Yet, in a very elegant study, Teixeira et al. showed that cells overexpressing SOD produce less hydrogen peroxide (11).

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The idea that increased SOD content could cause an imbalance in the metabolism of reactive oxygen species by neurons is not supported from a theoretical standpoint either. The dismutation of superoxide anion at pH 7.4, and the resulting hydrogen peroxide, still occurs in the absence of SOD. The role of this enzyme is to speed up this reaction by about 10 000-fold (12) to a rate close to diffusion-controlled, protecting tissues from oxidative stress by decreasing the steady state concentration of superoxide anion. Moreover, since the physiological concentrations of superoxide anion are orders of magnitude below those that would saturate SOD, and the reaction is essentially diffusion-controlled, extra copies of the enzyme should not necessarily affect the rate of hydrogen peroxide formation.

Superoxide anion is not a powerful oxidant per se, but rather a reductant under physiological conditions. In the presence of transition metals, superoxide and hydrogen peroxide produce hydroxyl radicals, one of the most powerful oxidants in nature. Its production results from the breakdown of hydrogen peroxide catalyzed by chelated transition metals (i.e. iron) in a Fenton reaction, and the role of superoxide anion (or an equivalent reductant) is to maintain iron in its reduced state (13,14). Therefore, the effect of increasing SOD should be to decrease (not increase) hydroxyl radical formation, preventing oxidative stress by decreasing the steady state concentration of superoxide anion.

We propose that increased SOD could have an indirect role in Down's syndrome; not in the etiology of the disease but rather in determining the correlation between the age of mothers and the frequency of Down's syndrome in their offsprings. Females are born with an enormous amount of viable oocytes (around 10^6) (15) which undergo apoptosis over their lifetime. Apoptosis is, to a large extent, prevented by SOD (16–18). In fact, in diseases such as familial amyotrophic lateral sclerosis (ALS) different mutations in the gene for SOD are supposed to be responsible for the increased neuronal apoptosis (19–21). Oocytes with an extra copy of chromosome 21 should be more resistant to apoptosis and, therefore, their proportion will increase with age because they are selectively protected. Thus, as females become older, the oocytes overexpressing SOD have a higher chance to become fertilized.

Surprisingly, Down's syndrome patients show increased neuronal apoptosis, which would not be consistent with an overexpression of SOD. One of the reasons for the increased neuronal degeneration in these patients could be that chromosome 21 also contains the gene for amyloid beta precursor protein (21q22.2). These patients will obviously have three copies of that gene, increasing the chances of its expression by 50%. This is consistent with the appearance of beta amyloid bodies and increased apoptosis, which are common symptoms in both Alzheimer's and Down's syndrome patients (22,23). Similarly, there are other critical genes in this chromosome which may contribute to other symptoms of this disease, including the high incidence of leukemia.

In summary, we propose that the overexpression of SOD is unrelated to the symptoms observed in Down's syndrome patients. Instead, an extra copy of this gene may protect oocytes from apoptosis without any toxic effects because in this case only two copies of chromosome 21 will be present. On the other hand, overexpression of other genes resulting from trisomy 21 (including but not limited to the beta amyloid gene) may be responsible for the phenotype of this disease.

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