Genetic Hearing Loss in Childhood and Oxygen Reactive Species

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Introduction

A medical knowledge revolution in different areas has been experienced. An unheard progression has been taking place in the understanding of the molecular basis of diseases, including deafness. Human Genome Project, completed in the beginning of this century, enabled quick advance towards the understanding of the fascinating biology of the auditory system and it also revealed new molecular mechanisms of hearing loss. Many "silence genes" became known. From then on, scientists progressed to Human Proteome. Currently, we are trying to understand and reveal the effects of DNA mutations in the formation and functioning of the effecting structures of auditory system - the proteins.

The genetic causes of hearing loss can be classified into syndromic and non-syndromic (isolated). Syndromic forms amount to approximately 30% of cases and the hearing loss is normally conductive or mixed. Over 400 syndromes have described deafness as an associated anomaly. Most of these diseases comprise ear embryological formation defects and approximately 40 genes implied in these syndromes have already been mapped in human genome, and more than half have already been cloned.

In such field, we made our first contribution by mapping the gene of Bjørnstad syndrome (congenital sensorineural hearing loss and pili torti) to locus 2q34-36. The symbol 2q means the long arm of chromosome 2 and 34 and 36 are two of the chromosome bands that are shown in the cytogenetic studies using specific dyes; the interval between them gives the locus of the gene to the syndrome, that is, the portion of DNA chromosome where the gene is located. Identification and cloning of gene is the later stage in which we can study in details only the chromosome interval in the search for mutations.

Oxygen Reactive Species

Free radicals (FR) or oxygen reactive species are molecules with one pair of unmatched electrons and, thus, highly reactive. They are constantly formed in aerobe cells, especially in mitochondria and erythrocytes. In normal conditions, they are removed by an efficient system of cell detoxification comprising antioxidant enzymes, glutathione, vitamins and microelements. However, when the production of FR supersedes the capacity of the antioxidant system, deleterious reactions can occur characterizing the condition known as oxidative stress.

FR result both from normal cell processes, such as aging, and pathological processes, such as trauma, radiation, chemical exposure and infection (FR are important in the bactericide activity of phagocytic cells). In some pathologies, such as sickle cell anemia, thalassemia and glucose-6-phosphate dehydrogenase deficit, oxidative stress is even greater.

Some research studies have also demonstrated that FR may act as stimulating factor of gene expression.

In Otorhinolaryngology, FR and their natural and pharmacological prevention are being broadly investigated, especially in cases of cochlear damage.

Oxygen Reactive Species Related to Hearing Loss

Bjørnstad syndrome (BS) is an autosomal recessive condition characterized by sensorineural hearing loss and pili torti associated with high production of cochlear and hair follicles free radicals. Hearing loss is congenital and of variable severity. Hair affection known as pili torti is characterized by twisted hair, a condition in which the hair shafts are flattened at irregular intervals and twisted 180 degrees from the normal axis, making the hair extremely brittle. Such characteristic is early recognized in childhood.

Cochlear and hair affections are related with mitochondrial metabolism affections and high FR production. It is believed that mitochondria have originated from aerobe bacteria that had symbiotic relation with primitive protoeukaryotes. Mitochondria are semi-autonomous organelles that auto-reproduce and are found in the cytoplasm of all cells. Each mitochondria is involved by a double membrane. The inner membrane is highly invaginated and its projections are named crests. Mitochondria are the sites of reaction of oxidative phosphorylation of the electron transporting chain, which results in the formation of ATP.

Protein BCS1L, with 419 amino acids, belongs to the family AAA ATPase associated with many different cell activities related with connection, degradation or unfolding of the protein structure. BCS1L is found in the internal mitochondrial membrane and facilitates the connection of complex III with complexes IV and I, assembling a respirasome supercomplex that facilitates the electron transfer required for ATP synthesis.

Gene BCS1L, responsible for SB, is located in chromosome 2q34-36. The mutation of this gene breaks down the connections of respirasomes, which is the basic respiratory unit in human mitochondria.

The clinical manifestations of Bjørnstad syndrome are not as severe as those related with other diseases of mitochondrial metabolism, such as Complex III Deficiency (OMIM 606104) and GRACILE Syndrome (OMIM 603358). The severe clinical manifestations of such syndrome, involving different organic systems, are related with gene mutations that break down the mitochondrial respiratory chain complex. Complex III deficiency is characterized by neonatal tubulopathy, encephalopathy and liver failure. GRACILE Syndrome is manifested by intrauterine growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis and early death.

BCS1L mutations modify connections of mitochondrial respirasomes, reduce the activity of the electron transporting chain and increase the production of oxygen

free radicals. Different clinical manifestations seem to be related with different energy tissue demands and specific sensitivity of each tissue to oxygen free radicals. The increase of free radical production is also related with the type of BCS1L mutation.

The mutation responsible for Bjørnstad syndrome increases the production of free radicals by Complex I generating oxidative stress in inner ear and hair follicle. Current models support other causes of increased reactive-oxygen in ototoxicity, including that both aminoglycoside antibiotics and excessive noise. Given the considerable self-renewal and proliferation required of hair shafts, robust anti-oxidant properties are likely required. In support of this hypothesis, it is noteworthy that a variety of hair abnormalities are often the presenting manifestation of mitochondrial disease.

The remarkable tissue-specific manifestations of Bjørnstad syndrome mutations hint at a shared mechanism for age-related loss of hair and hearing, since ageing, like Bjørnstad syndrome *BCS1L* mutations, increases reactive oxygen species.

In conclusion, massive production of knowledge related with genetic hearing loss in childhood has demonstrated important mechanisms related with cochlear physiology and cochlear pathological mechanisms. Moreover, knowledge can open new frontiers to prevention and management of hearing loss.

Recommended readings

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