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Review Article

Implication of Molecular and Cellular Mechanisms in Congenital Defects Sensitive to Folate Deficiency

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Abstract

The study of molecular mechanisms, signal transduction systems and intercellular communication mechanisms has undergone rapid development in recent years, leading to the incorporation of new critical concepts to understand how cells receive and coordinate signals from the environment and from other cells of the same organism, to control the processes of proliferation, differentiation, cell migration or apoptosis during embryogenesis. For these reasons, we feel motivated to carry out this review with the aim of making an approximation to the molecular and cellular bases of congenital defects sensitive to folate deficiency. A bibliographic review was carried out based on chronological and thematic criteria, both for scientific monographs and for articles published in national and international medical journals, in printed or online versions, in Spanish and English. The Google Scholar search engine was used and databases were consulted: PubMed, Medline, Bireme (Scielo, Lilacs and Cochrane). It is concluded that to continue advancing in this fascinating field, a better understanding of the functional interaction networks between genes and proteins, and their control by cell signaling systems, will undoubtedly be necessary.

Keywords: *Congenital/Genetic Abnormalities; Folic Acid; Transduction Signal; Routes of Communication Intercellular*

Introduction

According to the World Health Organization (WHO) a birth or congenital defect (CD) is any morphological alteration, biochemical or functional alteration, to occur at any stage of gestation and is detected at the time of birth or later. Since the point of view etiopathogenics are classified in: malformation, disruption, deformation and dysplasia. The primary structural defect that results from an inherent alteration in development is described as congenital malformations (CM).

CD can be multiple or isolated, and due to their magnitude they are distinguished into major and minor. The first have a functional import commitment to the life of the individual. Disruption, on the other hand, refers to the abnormal structure of an organ or tissue, as a result of the action of external factors that alter the normal development process, as a consequence of the rupture of tissues and genetically well-formed network of blood vessels. According to the etiopathogenic classification of Sprangel and Opitz, multiple CD can be

considered as: Sequences, Associations, Spectrum and Syndromes. The most commonly used reference guide at the international level for classifying CD is the International Classification of Diseases (ICD-10) published by the WHO [1-4].

According to WHO, 94% of the CD occur in developing countries, where mothers are more vulnerable to malnutrition macro or micronutrients. Different vitamins and minerals, collectively referred to as micronutrients, have a decisive influence on the health of the pregnant woman and on embryological development. Folate plays in a crucial role in the epigenetic regulation of embryo - fetal development and has been shown to its deficiency is associated with the appearance of different CD, including described in the literature: the defects of the neural tube (NTDs), conotruncal heart defects, Down syndrome, non-syndromic orofacial clefts and gastroschisis [5-9].

Methods

A bibliographic review was carried out based on chronological and thematic criteria, both for scientific monographs and for articles published in national and international medical journals, in printed or online versions, in Spanish and English. The Google Scholar search engine was used and the databases were consulted: PubMed, Medline, Bireme (Scielo, Lilacs and Cochrane) in order to make an approximation to the molecular and cellular bases of the deficiency-sensitive CD of folates. Those articles that allowed free access to full texts were selected according to their relevance and most recent publication date.

Development

Many are the genes that are involved in development and act during the morphogenesis stage. Cellular processes obey complex gene interactions and regulations that occur in a limited time and space, so that CD can be due to gene, chromosomal or genomic mutations that affect the development process and that can be expressed with extremely dysmorphological heterogeneity variable [10].

The communication intercellular is the process by which cells exchange messages chemicals that modulate intracellular operation and give rise to specific responses designed to promote adaptation of the entire organism in a changing environment. Communication systems and cellular signaling are fundamental in the control of gene expression and function of proteins, so the repertoire of transduction via involved in the origin of CD is increased [11].

Intercellular signaling systems are essential in the control of gene expression and protein function. These systems will control where, when, for how long and for how long ribonucleic acid (RNA) molecules are expressed. In the case of proteins, they also control changes in location, the trafficking of proteins within a cell, how they degrade, and the functional interactions they establish. Consistent with this critical role in the function of organisms, it is estimated that more than 20% of the genes in the human genome encode proteins involved in signal transduction [12].

Genetic and cellular bases of NTDs

NTDs are the most common and severe CD of the central nervous system (CNS). They result from an embryonic failure in the closure of the neural tube that can occur at any level of the embryonic axis. Despite the long history of etiological studies, the molecular and cellular mechanisms underlying NTDs remain poorly understood [13].

There is evidence that the closure of the neural tube starts and fusioning intermittently at different locations, through site genetic mechanisms - specific, which play a role leading several genes that are part of the metabolic pathway of folate [14-17].

In an extensive investigation carried out in Ireland in 2012, 1441 SNPs were studied in 82 candidate genes for NTDs (selected from the metabolic pathways of FA, from vitamin B12 and from mouse models with NTDs), about 70 polymorphisms were found in 30 genes that were associated with this type of CD. The 10 strongest associations (p-value range: 0.0003 - 0.0023) were found in nine genes (MFTC,

CDKN2A, ADA, PEMT, CUBN, GART, DNMT3A, MTHFD1) and the MTHFR gene, whose polymorphisms are a known risk factor for NTDs, was included [18].

Genetic studies on NTDs have focused primarily on the MTHFR gene and other genes involved in folate metabolism, based on the fact that preconception supplementation with folic acid (FA) reduces the risk of NTDs by between 50 to 70% [19].

There is scientific evidence that shows that the presence of single nucleotide polymorphisms (SNPs) in genes that encode enzymes of folate metabolism can affect the biochemical indicators of the state of FA in humans. To date, the SNPs most studied are rs1801133 (C677T) located in exon 4 of the gene, which consists of the substitution of cytosine for thymine at codon 222, which causes the substitution of alanine for valine at nucleotide 677 and rs1801131 (A1298C) polymorphism where the substitution of adenine by cytosine occurs at position 1298 of the gene that codes for this enzyme, resulting in a change of glutamic acid for alanine at nucleotide 429.

The homozygous C/C allelic combination represents the wild genotype of the C677T polymorphism, the heterozygous C/T combination and the homozygous T/T, represent genotypes that originate enzymes with a reduction of their reductase activity by 30 and 60% respectively, while the mutation on A1298C is associated with a reduction in enzyme activity levels, but not as severe.

Different studies have evaluated the association between polymorphism C677T of the MTHFR and concentrations of FA, finding differences in concentrations in the different genotypes (CC > CT > TT) and particularly the homozygous genotype T/T increased by 2.24 times the probability of presenting low concentrations of FA [6,8,14,20-22].

In research in mouse models, a large repertoire of more than 200 genes required for the closure of the neural tube has been described. These genes are involved in a wide variety of cellular mechanisms [13].

The Hedgehog (Hh) pathway plays a fundamental role in the development of the CNS of vertebrates. The function attributed to it par excellence is to specify the cell types of the ventral region of the neural tube, resulting in the formation of the dorsal/ventral pattern of the neural tube. But not s or controls specification but regulates cell proliferation and survival through the regulation of the cell cycle and gene expression antiapoptotic.

The gene that codes for Hh was identified by mutagenesis studies in the Drosophila fly, where the mutant embryos showed defects in the cuticle and their name “hedgehog” derives from the disorganized tip pattern of the exoskeleton denticles. In vertebrates, the pathway is made up of the Sonic (Shh), Desert and Indian Hedgehog ligands, which when they bind to the Patched membrane receptor, this releases the Smoothened protein to migrate towards the primary cilium (sensing organelle of different extracellular stimuli that protrudes on the apical membrane of almost all somatic cells) and triggers the reactions that culminate in the activation of its Gli effectors. Gli proteins are transcription factors that move from the primary cilium to the nucleus to activate or repress the transcription of their target genes.

The overactivation pathway Hh and the loss of function in the non-canonical pathway polar cellularity planar (Planar cell polarity: PCP) are potent causes of NTDs. It has been shown that both mutations in the gene encoding the transmembrane receptor PTCH1 that cause a decrease in the activity of the SMO protein and the abolition of inhibitory phosphorylation sites for protein kinase A in the Gli2 gene, cause [23].

The PCP cell signaling pathway is a complex molecular mechanism that provides the cell with a coordinated polarized orientation necessary for numerous developmental processes, including its directional movements during gastrulation and neurulation in vertebrates [13].

Animal studies have demonstrated the fundamental role of the PCP pathway in mediating the morphogenic process called convergent extension, during the formation of the neural tube. Alterations in the members of this pathway lead to the appearance of NTDs in vertebrate models, constituting novel candidates for NTDs in humans [24].

Genetic and cellular bases of congenital heart disease

Although congenital heart disease (CHD) is a frequent cause of morbidity and mortality worldwide, the genetic bases and molecular mechanisms that underlie them are, to a large extent, to be determined.

In recent decades, the great advances made in molecular genetics technology have begun to be applied to the field of pediatric cardiology, which has allowed the identification of many genes that are involved in the primary etiology or that are significant risk factors in the development of cardiovascular congenital defects [10,25].

To date, there is evidence of mutations in more than 60 genes that are related to the appearance of different types of CHD. Among them, those that code for transcription factors that participate in the cardiogenesis process are the ones most frequently associated with CHD, evidence of the crucial role that these transcription factors play in the process of cardiac morphogenesis and in the origin of this type of heart disease [26-29].

Septal defects are the most common type of CHD, representing 50% of these. In both animal models and in the study of affected families, various molecular aspects of septation defects provide information that coincides in identifying specific genes. The current knowledge of the importance of transcription factors in this group of CHD is remarkable: NKX2-5, NKX2-6, TBX1, TBX5, TBX20, HAND2, GATA4, GATA5 and GA-TA6. These transcription factors, which are expressed early in cardiac lineage cells, also regulate the expression of contractile protein genes in cardiomyocytes.

In late stages of cardiac development, mutations in each of these genes lead to severe congenital heart defects such as conotruncal (NKX2-5, TBX1, TBX20 and GATA6), bicuspid aortic valve (GATA5 and NKX2-5), septation defects atrial and ventricular (NKX2-5, NKX2-6, TBX1, TBX5, TBX20, GATA4, GA-TA6), conduction defects (NKX2-5), right ventricular hypoplasia (HAND2), tricuspid atresia and Ebstein's anomaly (NKX2- 5) [25].

Conotruncal CHD, on the other hand, comprise a subgroup of congenital malformations of the outflow tract of the heart and the great arteries, which include: the patent artery trunk, interruption of the aortic arch, transposition of the great vessels, double outlet of the right ventricle, conoventricular septal defects, tetralogy of fallot and pulmonary atresia with ventricle septal defects (VSD).

These congenital malformations share a common embryological origin and structural, as derived from cell or the cardiac neural crest and the second heart field (SHF: second heart field). Congenital conotruncal defects represent approximately 20-30% of all types of CHD in humans [30,31].

The genetic etiology of some of these CHD began to be seen when studying the 22q11.2 microdeletion syndrome, which causes a partial monosomy of the long arm of chromosome 22, which includes DiGeorge syndrome, facial velocardium and conotruncal-facial anomaly. This is the most frequent type of deletion and the second cause of CHD associated with syndromes, after trisomy 21. This syndrome of contiguous genes is phenotypically characterized by malformations associated with defects in the fourth branchial arch, and in the third and fourth bursa pharyngeal, which contribute to the formation of the thymus, parathyroid and heart.

Among CHD, the most common is the persistence of the trunk arteriosus (absence of septation in the outlet cone, and its division into aorta and pulmonary artery), but it also includes tetralogy of Fallot, interruption of the aortic arch and double outlet ventricular [32].

The deletion spans about 3 Mb and contains 30 genes, including CRKL, TBX1, TXNRD2, and GP1BB, which are expressed in the pharyngeal arches. This chromosomal microdeletion is responsible for approximately 12% of cases with conotruncal CHD [30-33].

A relationship has recently been found between GATA6 gene mutations with outflow tract defects, specifically, with patent ductus arteriosus and tetralogy of Fallot. GATA6 is a member of the FT GATA family, its expression and function frequently spliced with that of GATA4. The latter has already been related to different CHD; However, the role of GATA6 in these CHD is barely being elucidated; it is known that this transcription factor regulates the expression of the genes that encode the neurovascular guide protein Semaphorin 3C and its receptor Plexin A2 [34].

The Nodal/TGF (Transforming Growth Factor) signaling pathway has an important effect on the differentiation of human pluripotent cells. The Smad 3 gene is a key intracellular messenger in the regulation of the Nodal/TGF pathway that has an important role in embryonic development and particularly in the development of the cardiovascular system.

Recently, researchers from the Harbin Medical University, in the People's Republic of China, identified two polymorphisms of a single nucleotide SNPs (SNP: single nucleotide polymorphism) in the LEFTY2 gene (rs2295418 and rs360057), significantly associated with the risk of developing. LEFTY is an important transforming growth factor with negative regulation function in the Nodal/TGF signaling pathway that inhibits the proliferation and cell differentiation of embryonic stem cells into cardiomyocytes, resulting in different types of CHD [35].

It has been shown that the Notch pathway also regulates the cell differentiation of the proepicardium and the adjacent pericardial mesoderm, so that the inhibition of its expression in the epicardial lineage inhibits the formation of the coronary arteries, reduces the proliferation of cardiomyocytes and the thickness of the myocardial wall. Mutations in the gene JAG1 or inhibiting signaling Notch in SHF causes different CHD, primarily of the aorta and the outflow tract [36].

Genetic and cellular bases of Down syndrome

Down syndrome (DS) is the first chromosomal origin syndrome described and is the most common cause of mental retardation of genetic origin.

The trisomy that causes DS can be total or partial. In 95% of the cases, DS is due to a total, free or regular trisomy of HSA21 (Homo Sapiens Autosome 21), with Karyotype: 47, XX, + 21 or 47, XY, + 21, and in the rest it is describe aberrations chromosomal structural (translocations Robertsonian between acrocentric chromosomes group D or G (Karyotype: 4 6, XX or XY, rob (D or G; 21) (q10; q10), + 21, isochromosomes of l long arm of HSA21 (Karyotype: 46, XX or XY, + 21, i (21) (q10), Partial trisomy of the region 21q22.3 (Karyotype: 46, XX or XY, dup (21) (q22.3) and the chromosomal mosaicism, which s and defined as the presence of two or more cell lines different in the same individual (Karyotype: 47, XX or XY, + 21/46, XX or XY and corresponds to 1 - 3% of all cases [7,21,25].

The fundamental cause of trisomy 21 is the meiotic non-disjunction of HSA21 that in 90% of cases occur in oogenesis. During meiosis, several genes are activated, such as SMC1β and STAG3, which code for cohesin enzymes, essential for centromeric cohesion.

Other genes such as Sgo1, CHl4, Iml3, are expressed at the beginning of anaphase II. Other genetic factors that are associated with the non-disjunction of HSA21 are the alteration in the meiotic recombination pattern and the abnormal location of the chiasm [25,37,38].

There is sufficient scientific evidence that the absence of recombination along the HSA21 is related to the risk of nondisjunction, regardless of maternal age, particularly in meiosis I. The PRDM9 gene is related to the location of recombination events and is associated with significant changes in the frequency of recombination.

On the other hand, the formation of the chiasm usually takes place in a medial position of the chromosomes, which confers the appropriate balance necessary in segregation, but the occurrence of the chiasm near the centromere or telomeres generates instability and makes HSA21 susceptible to alterations in segregation and subsequent nondisjunction. Different population studies revealed that the

formation of a telomeric chiasm is a risk of nondisjunction (ND) from HSA21 in meiosis I, even in young women, while a chiasm very close to the centromere increases the probability of DN in meiosis II [37-39].

Molecular studies in patients with partial trisomy of the Hsa21 have delimited delimits I do a region of a of 1.6 Mb called 'critical region for DS".

In this region, the highest recombination rate is recorded in bands 21q22.13 - 21 q22.3, where several genes show a high degree of methylation in CpG islets (both in normal and trisomic fibroblasts), suggesting that this region plays an important role not only in nondisjunction, but in the complex genomic and epigenetic interactions involved in the pathogenesis of DS.

However, the concept of critical region is currently the subject of scientific controversy, since several studies indicate the occurrence of DS in association with chromosomal regions outside this region, which is why it is considered that the characteristic phenotype of these patients is it is due to a complex overexpression and interaction of several genes located throughout the HSA21, rather than to the direct correlation between a fragment of it and phenotypic traits [21,25,40].

The cerebral and cerebellar dysmorphies of DS include decreased number of neurons and granular cells, cerebellar volume, dendritic malformations, and synaptic abnormalities. The Ts65Dn mouse model is trisomic for 88 orthologous genes, out of the classic 161 coding genes present in HSA21, which makes them exhibit cognitive deficits and brain dysmorphological alterations similar to those observed in people with DS.

Researchers found that l to acute stimulation via Hh can correct the deficit mitogenic in neurons cerebellar precursor and normalize the structure of the cerebellum in these mice, whereas chronic increase pathway regulation Hh normalizes some effects of development. These results indicate that the decreased response to some of the members of this family of proteins in trisomic cells and tissues contributes to the presence of various phenotypic aspects in patients with DS [41].

Genetic and cellular bases of non-syndromic orofacial clefts

The term nonsyndromic orofacial clefts (OFCs) refers to the presence of a cleft lip and/or palate without other associated CD, which is manifested by an incomplete separation between the oral and nasal cavity constituting as the more frequent craniofacial CD.

In 1942, Fogh-Andersen classified OFCs into: cleft lip (CL) (LL), cleft palate (CP) (PH) and LL CL with CP PH, later, in the first decades of the 21st century and considering different embryological and developmental factors, as well as different genetic studies, OFCs were classified into two groups: CL LL with or without non-syndromic cleft palate PH and isolated non-syndromic cleft palate PH. The category of CL LL with or without non-syndromic CP PH includes individuals with LL CL only, which can be unilateral or bilateral, and CL LL accompanied by CP PH [42,43].

Prior to the era of the study genome - wide association (GWAS: Genome-wide association studies) genetic studies of OFCs HOFNS were limited to samples based on clinical, however, they allowed the identification of a susceptibility gene for these CD, the IRF6. To date, there is evidence of the identification of three SNPs (rs642961, rs861020 and rs10863790) in the proximity of the IRF6 gene, most of them described in cases with European or Asian ancestry.

The advent of GWAS has allowed the identification of 29 SNPs and multiple susceptibility genes for OFCs, among these loci are 1p36.13, 1q32.2, 2p21, 3p11.1, 8q21.3, 10q25.3, 13q31. 1, 17p13.1 and 20q12. [42,44,45].

In a case-control study based on GWAS, with the aim of elucidating the genetic architecture of non-syndromic CL/CP LL/PH and identifying new susceptibility loci. Sun and collaborators [46] found several previously described SNPs, however, they identified a new poly-

morphism associated with OFCs in the Chinese population, the (rs8049367) with locus at 6p13.3, which is located 50 kb of the CREBBP gene, a transcription factor that plays a crucial role in embryonic development, as it is a coactivator of the P300 protein.

The superfamily of transforming growth factors Beta (TGFβ: Transforming Growth Factor Beta) plays an important role in embryonic development. It has been shown that knock-out mice to TGF β 3 have OFCs and to which this control protein the differentiation of epithelial cells to mesenchymal on the medial part of the two palatal processes.

To this superfamily belong morphological bone protein (BMP: Bone Morphological Proteins), growth factors involved in the gastrulation, the organogenesis and growth embryonic and postnatal growing. The importance of BMPs in palatogenesis began to be evidenced by research models with mice in which OFCs was induced by application of retinoic acid and was associated with decreased expression of BMP2.

On the other hand, a high expression of BMP2 protein was found in the mesenchyme adjacent to the midline during palatal fusion. Therefore, these studies allow us to conclude that the mesenchymal proliferation mediated by BMP2 is a key event in the palatogenesis process, where the expression of several genes of the Notch pathway has also been detected, such as Jagged2 and Hes1. R atones Mice with homozygous mutations Hes1 -/-, presents had premature elevation and a horizontal reorientation of palatal, which generated CP or one PH [47,48].

Some studies carried out during the embryonic development of the mouse have revealed the connection between mutations of different genes of the Notch signaling pathway and the presence of different congenital craniofacial malformations, such as cleft lip/palate, which shows that this signaling pathway could have an important role in the formation of the branchial arches, protagonists in the morphogenesis of the face and neck [49].

Genetic and cellular bases of gastroschisis

This term gastroschisis (GS) literally means “split or open stomach”, so it is not the most appropriate, since it is actually the anterior abdominal wall that is open and not the stomach. It is defined as a visceral herniation through a defect to the right side of the abdominal wall, with an intact umbilical cord and not covered by membranes. The definition excludes omphalocele.

However, until version 9 of the international statistical classification of disease and related health problems (ICD) both CD were included under one code: 7567. Only in the version 10 (ICD-10) these two main defects have separate codes: Q79.2 for omphalocele, Q79.3 for GS. At the beginning of the 2000s, the classification of simple and complex GS began to be introduced, the first is reserved for cases that have an isolated defect of the abdominal wall with intestinal protrusion, while complex forms refer to those that they coexist with necrosis, atresia, perforation, or volvulus [50-52].

The etiopathogenic mechanisms of GS are not fully elucidated, historically a mechanism of vascular disruption has been proposed due to agenesis of the right omphalomesenteric artery, which causes infarction and necrosis of the base of the cord, allowing visceral extrusion.

Other mechanisms that have been invoked are rupture due to weakness of the anterior abdominal wall caused by normal involution of the right umbilical vein and the occurrence of thrombosis underlying the umbilical ring at this site of involution, or rupture of an omphalocele before the anterior abdominal wall to fold.

However, recent hypotheses focus on the process of closure of the ventral wall, the development of the umbilical ring and the failure of the sac, the Yolk duct and the Yolk vessels, to initially join the allantois and subsequently the stem bodily.

Among the polymorphisms that have been associated with GS are those related to arterial hypertension (HPT), which supports the hypothesis of an etiopathogenic mechanism associated with an underlying vascular disruption. However, the increase in the frequency of GS in recent decades presupposes that not only are there genetic factors involved in its origin, but that its etiology can be explained by a gene-environment interaction [50,52-54].

Different family studies suggest an underlying genetic susceptibility for GS [9,50,55].

In a population-based study carried out in California, USA, 75 genetic variants were investigated in 20 genes of 228 infants with this CD and 11 polymorphisms were associated with a high risk of GS and four associated with a decreased risk, for genotypes with variants heterozygous or homozygous. The high risk for this CD was observed in cases with polymorphisms in genes related to HPT HTN (NOS3 and ADD1) and cell-cell interaction (ICAM1, ICAM4, and ICAM5). While gene variants in GNB3 and NAT1 were associated with a decreased risk for GS [9].

The NOS3 gene involved in the conversion into the cytosol or cytoplasm of arginine or nitric oxide (NO), which plays important physiological roles as a mediator of vascular tone, important physio mediator will or logical of vascular tone, and also contributes crucial roles in regulating endothelial migration, angiogenesis, and vascular remodelling, which contributes in addition to s the adjustments makes it or n of the migration endothelial ng, angiogenesis and remodeling vascular, while the NO or oxide igniter seems to function as a maintenance factor for several integrins that are important regulators of cell migration and angiogenesis. These processes are likely important to the development of GS. is a factor of maintenance for many integrins are important regulators of migration or cell n and angiogenesis, processes great importance in the pathogenic ENESIS GS.

Meanwhile, the ICAMs are a family of proteins from the cell surface that are encoded by three genes (ICAM-1, 4 and 5) with loci in 19p32 and which are to n - related to cell-cell interaction. or n intercellular. Cell adhesion molecules play an important role in the coordinated regulation of endothelial cell migration during angiogenesis. The mol é particles of accession or cell n play an important role in the regulation coordinated the migration will or cell endothelial during angiogenesis [54].

Considering the duality of a possible vascular/thrombotic pathogenic mechanism in the genesis of this developmental disorder, Makhmudi., *et al*. [56] studied three prothrombotic polymorphisms in 46 patients with GS and in 89 ethnic-matched controls.

Of the SNPs studied, only MTHFR C677T showed a statistically significant association with GS (OR: 2.1, 95% CI: 1.13–3.86; p =. 018), in addition, the frequency of the T allele was higher in patients born to mothers less than 25 years of age than in those with maternal age greater than or equal to 25 years (p = . 069) with an OR of 2.7 (95% CI C: 0.90 - 8.07), so the group of researchers concluded that SNP C677T is a susceptibility factor for GS in Indonesia and that the increased risk for the offspring of younger mothers supports the thrombotic pathogenic model in this CD.

The transforming growth factor Beta (TGFß) are related to many processes development, including formation of the anterior abdominal wall. Embryos of chicken double knockout TGFß2 (-/-) TGFß3 (-/-) and TGFß2 mutants (-/-) TGFß3 (+/-) had defects in the anterior wall of the abdomen (DPA), while mutant embryos TGFß2 (+/-) TGFß3 (-/-) showed a normal melting of the abdominal muscles, concluding that TGFß2 gene that is critical in the formation of the anterior abdominal wall [57].

US investigators, found increased expression of the TGFß3 gene, in the intestine of animals with hypertension nonocclusive mesenteric venous, concluding that the TGFß3 gene contributes to intestinal dysfunction, increased shrinkage at the cellular level and increased of contractile gene expression at the molecular level, and that this hypercontractile response may play an important role in abdominal wall defects [58].

Conclusions

The study of the molecular basis of CD with high frequency in humans, of the signal transduction system and of the mechanisms of intercelular communication has experienced a remarkable development in recent years. To continue advancing in this fascinating field, a better understanding of the functional interaction networks between genes and proteins, and of their control by cell signaling systems, will undoubtedly be necessary.

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