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ROLE AND DYSFUNCTION OF THE EMBRYONIC DEVELOPMENT PATHS AND POST-NATAL PERSISTENCE. WNT / BETA-CATENINE SIGNALING ROAD INVOLVEMENT

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ABSTRACT

Introduction: Gene signaling is an essential input for successful embryonic events. Through gene transport pathways, such as the Wnt / β-catenin pathway, embryonic developments are orchestrated harmoniously with the other physiological functions. **Objective:** This is an integrative literature review in order to analyze the scientific evidence the participation of the Wnt family in embryonic events. **Methodology**: An extensive review was performed on the Lilacs, PubMed and SciELO databases with full articles published in Portuguese, English and Spanish. **Results and Discussion:** Wingless (Wnt) belongs to the group of molecular flags, from a family of genes that act in various embryonic processes. The phenotypes of mutant embryos revealed that these genes act on the morphogenesis of numerous tissues and organs. Wnts are part of a family of signaling proteins and participate in autocrine and paracrine mechanisms, determination of gonads, cancer, glioblastoma, as well as the pathway involved in cellular communication, environmental micro-modulation and immune response. **Conclusion**: Cellular and molecular events depend on signaling pathways that are controlled by the Wnt family of genes, which participate in prenatal and postnatal embryonic events.

Keywords: Wnt, signaling, carcinogenic, embryonic development.

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INTRODUCTION

The embryonic development consists in several events that lead the zygote to the formation of a complete organism[1]. In this process, a cell must go through several decisions until it reaches a differentiated state with defined functionality. Embryonic development is governed by signaling pathways and organized by the expression of certain temporally and spatially controlled genes, resulting in the standardization of the embryo[2].Gene signaling is a primordial contribution for embryonic events to occur successfully.[3] During embryonic development, agents use communicating junctions with a phenomenon called chemotaxis. Through gene transport pathways such as the Wnt / β-catenin pathway, embryonic developments are orchestrated harmoniously with the other physiological functions[4]. Such pathways participate in prenatal events and it was observed that their persistence occurs in the postnatal phase[5]. Developmental potential, molecular and cellular factors are also included, however persistence is not inherent in activation of signaling pathways. The Wnt / β-catenin pathway is always present in human physiology leaving the comparison threshold of its gestational and postnatal purpose very similar[3].

The objective of this work was to conduct a survey on the participation of Wnt and to relate its function and dysfunction in embryonic cellular signaling events and human physiology.

METHODOLOGY

The data search was performed in the following databases and online libraries: Lilacs, PubMed and SciELO, SCIENCE DIRECT, SPRING, SCHOLAR, AGUS, TANDFONLINE, THIEME-CONNECT. For this, the following health descriptors were used: Wnt, signaling, carcinogenic, embryonic development in Portuguese, English and Spanish. Inclusion criteria were: complete articles published in Portuguese, English and Spanish and corresponding to the research question. Thirty articles were located and, after applying the inclusion criteria, 22 journals were selected, which comprised the study sample and then proceeded to the exploratory reading of all the material.

RESULTS AND DISCUSSION

WNT'S ROLE IN EMBRYO EVENTS

The Wingless (Wnt) belongs to the family of molecular flags, a family of genes that act in various embryonic processes[5]. These agents participate in polarity, proliferation and cell death during embryonic development and homeostasis[8, 10 and 12].

Composed of cysteine-rich glycoproteins, Wnt binds to seven-pass transmembrane proteins-Frizzled (Fzl), which has cysteine-rich extracellular domain, CysteinRich Domain (CRD) with recognition site via β-catenin. These flags are grouped into classes I Wnt1, Wnt8, Wnt8b, and Wnt3a, responsible for the activation of the canonical pathway involved with cell fate and proliferation and the phosphonositides; class II: Wnt4, Wnt5a, and Wnt11 that perform non-canonical transduction signals responsible for movement and polarity[13].

Wnt can trigger cytoplasmic variations. In its absence, β-catenin remains low due to the interaction of cadherin at the intercellular adhesion sites or by degradation in the proteosome as a function of β-catenin phosphorylation as a result of GSK3β/Axina/APC[8].

Gene knockout in mice led to inactivation of most Wnt genes. The phenotypes of mutant embryos revealed that these genes act on the morphogenesis of numerous tissues and organs. For example, gene inactivation due to Wnt-4 suppression causes absence of kidney[14], masculinization in females, absence of Müller canal and continued development of Wolff canal as defects in mammary gland morphogenesis during pregnancy[15]. The Wnt-7A also has a pleiotropic effect, which includes female infertility due to failure of Müller's canal regression and delayed morphological

maturation of cerebellar glomerular rosettes[16 and 17].

In mammalian embryos, the zygote goes through successive symmetrical divisions, resulting in morphologically similar blastomers. In the blastocyst phase, the embryo undergoes cavitation and the first cell differentiation occurs, in which the blastomers lose totipotency, forming two cell populations: the trophectoderm and internal cell mass[18].

The cells of the internal cell mass in E4.5 differ in two populations: the epiblast, which is the cell that continues to express Nanog, and the primitive endoderm, the epiblast cell layer, no longer express the pluripotency marker. Nanog and now express Gata6[19]. Primitive endoderm gives rise to visceral endoderm which is divided into visceral, parietal and distal endoderm. The distal visceral endoderm expresses Dkk1, an antagonist of the Wnt / β-catenin pathway, generating a signaling gradient that aids in the formation of important structures for the epiblast gastrulation process[20].

Epiblast is formed by the cell population that continues to express Nanog, thus maintaining its pluripotency[18]. It gives rise to the three germ leaflets during gastrulation, which begins at E6.25, when part of the epiblast cells undergo the epithelial-mesenchymal transition process and migrate to form the primitive line. Priming line formation is controlled by the Wnt / β-catenin and FGF pathways[20].

Formation Anteroposterior axis

The formation of the anteroposterior axis depends on the signaling gradient of the Wnt / β-catenin pathway, and on the signaling of the extraembryonic ectoderm and distal visceral endoderm[18]. The importance of this extra-embryonic tissue for embryo standardization was evidenced by its removal, leading to the absence of expression of posterior region markers and primitive line such as Crypto, Nodal and Brachyury (Bra(T))[5].

Wnt / β-catenin signaling is also essential for the formation and maintenance of the primitive line and therefore for the definition of the posterior portion, as well as the expression of its antagonists is important for the formation of the anterior region[22].

Embryo Bodies

The embryo bodies (EC) are aggregated and formed from embryonic stem cells (ESC), capable of reproducing early stage embryonic events[23]. Isolated from embryoblast, ESC when cultivated maintains its undifferentiated state. They are pluripotent and can differentiate, perform self-renewal, express pluripotency markers, give rise to the three germ leaflets and form teratomas. Because they are able to originate any cell in an adult organism, EC formed from ESC are widely used as models for the study of embryonic development.[21]

EC standardization

Unlike the embryo, the EC is formed only by cells of the blastocyst's internal cell mass and is therefore devoid of signaling from extraembryonic tissues that pattern the body axes in the embryo. Therefore, the formation of the different cell types in the EC is expected to occur without an apparent global organization. However, there is evidence that ECs have a pattern and studies show that they even have the ability to standardize important markers for gastrulation, such as BRA (T) e SOX17, and standardization of the Wnt / β-catenin pathway, however, the factors leading to its standardization have not yet been fully elucidated[21].

Wnt/β-catenina way

It is an important signaling for the embryonic development of all metazoans[28], which plays a role in embryo standardization and synaptic differentiation, and loss of gene function in this pathway can lead from embryo death and central nervous system abnormalities to kidney and limb developmental defects[5]. When it is inactive, the destruction complex is active and phosphorylates β-catenin. The destruction complex is formed by the proteins AXIN, APC (AdenomatouPolyposis Coli); CK1

(CaseinKinase 1) e GSK3 (GlycogenSynthaseKinase 3). Once phosphorylated, β-catenin is recognized by β-TRCP and promotes ubiquitination. When the Wnt / β-catenin pathway is active, Wnt / β-catenin ligands bind to the Frizzeld (FZD) receptor and coo-receptors LRP6/5 (Low-densityLipoprotein Receptor-relatedProtein 6/5), forming a complex. This complex recruits Dishevelled protein. (DVL), leading to activation and recruitment of the destruction complex to the receptor site (MacDonald et al., 2009)[29]. Target genes of the Wnt / β-catenin pathway vary by cell type. This pathway is capable of regulating in-pathway genes and target genes related to cell proliferation, cell polarization and cell destination decisions[5 and 29].

In the embryo, polarization of the Wnt / β-catenin pathway plays an important role in defining the anteroposterior axis[30]. Deletion of β-catenin in the embryo leads to Gastrulation failure, absence of primitive line and consequently failure of mesoderm formation[32].

Alterantion of Wnt / beta-catenin Signaling Pathway

The Wnt pathway interferes with the embryonic development of vertebrates and invertebrates, playing its role in symmetry, organogenesis and cellular fate[1]. It also plays a very important role in tissue homeostasis, through stem cell self-renewal and proliferation, as well as their differentiation and migration[31]. It is widely known that abnormal activation of the canonical Wnt (or Wnt / β-catenin) pathway plays an important role in the development of various types of cancers. More recently it has demonstrated its role in adrenocortical tumorigenesis[**24**].

Mutations in exon 3 of the CTNNB1 gene encoding the β-catenin protein decrease the degradation rate of this protein, keeping this pathway constitutively activated. Mutations in this gene are frequently found in up to 36% of adult patients' TACs (adrenocortical tumors), predominantly in non-secretory tumors and with similar frequencies in AAC (adrenocortical adenomas) and CAC (adrenocortical carcinomas)[1]. CTCNB1 mutation carriers and / or abnormal cytoplasmic and nuclear β-catenin accumulation show more aggressive tumor phenotype[26].

In the CAC study in the cohort of French patients, in which tumors were subdivided into carriers of CTNNB1 or TP53 gene mutations, both had poor prognosis. The mutations were mutually exclusive because none of the CACs analyzed carried mutations simultaneously on these two genes[26]. It is noteworthy that the majority of CAC analyzed were sporadic and mutations in the TP53 gene were somatic. More recently, a large-scale sequencing study by the same French group found a recurrent mutation in the ZNRF3 gene. The protein encoded by this gene is a cell surface ubiquitinaligase that negatively modulates the Wnt / β-catenin pathway, promoting reduced LRP5 / FRIZZLED receptor activation. Inactivating mutations and homozygous deletions detected in this gene induce activation of the Wnt / β-catenin pathway[27].

Pediatric TAC scan initially revealed mutations in the CTNNB1 gene in only 6% of the tumors and all patients had the P53 p.R337H mutation. There is an association between the presence of mutations in CTNNB1 and risk of death. However, the number of cases with this mutation was too small to generalize this finding. In addition, it was identified that diffuse β-catenin accumulation in the cytoplasm and / or nucleus in 71% of the TACs. Therefore, abnormal β-catenin accumulation was present in most tumors, even in those without CTNNB1 mutations[24].

In tumors, decreased expression of genes encoding Wnt inhibitor proteins, such as DKK3, SFRP1 and AXIN1. On the other hand, there was also increased expression of WISP2, one of the targets of β-catenin[24]. Based on these findings, we hypothesized that the activation of the Wnt / Beta-catenin pathway observed in most pediatric TACs is not due to mutations in CTNNB1, but to other changes in gene

expression of pathway regulators by mechanisms that are still being unraveled[25].

Relation of the Wnt pathway to the albumin pathway

The relationship between Coup-tf2 and the Wnt / β-catenin pathway varies according to the cell type or signaling level analyzed. The effect of Coup-tf2 on pancreatic β cells and observed that there was a decrease in expression of β-catenin and other Wnt / β-catenin pathway genes such as c-Myc, Gsk3 and Axin2 in the absence of COUP-TF2. Increased expression of β-catenin and Cyclin D1, a pathway target gene, may have a positive relationship between the two factors, in which the absence of COUP-TF2 leads to reduced pathway signaling. A positive relationship between Coup-tf2 and the Wnt / β-catenin pathway was observed in studies performed on β-catenin-silenced preadipocytes, which showed a reduction in Coup-tf2 expression. It was also observed that in mesenchymal stem cells with COUP-TF2 deficiency promoted Wnt10b increase, and that COUP-TF2 silencing led to induction of β-catenin expression. An important role of COUP-TF2 is in defining angioblasts as to arterial or venous fate. In angioblasts where the Wnt / β-catenin pathway is active, Sox17 expression activates the Notch signaling pathway, resulting in the arterial phenotype, suggesting that some Sox factor below the Wnt / β-catenin pathway may be interacting with COUP- TF2, activating it, and thus inhibiting the Notch pathway[41].

Interaction of Wnt pathway

The interaction of Dpr proteins with Wnt signaling was verified by two yeast hybrid tests using the Dsh protein as bait. In these assays, it was found that the Dpr protein has a PDZ-binding domain that mediates its interaction with Dsh through its PDZ domain. This interaction was demonstrated by Dsh co-precipitation assays with different Dpr delivery constructs, which contained different domains of this protein. [33 and 34] The discovery that Dpr1 can interact with the Wnt pathway not only via the Dsh protein, but also via the factor Tcf-3, another component of the Wnt signaling pathway[35].The Dpr1 protein, besides being present in the cytoplasm, can also be observed in the nucleus of some cells, interacting with the β-actin - LEF1 complexes, controlling the cell cycle progress[36].

WNT / BETA-CATENINA SIGNALING WAY

Wnts are part of a family of signaling proteins and participate in autocrine and paracrine mechanisms. These proteins interact with Frizzled receptor, and an LRP co-receptor and trigger cascade reaction leading to β-catenin accumulation in the cytoplasm. This pool is displaced to the nucleus promoting interaction with transcription factors such as TCF / LEF1, which activates the expression of target genes such as c-Myc and cyclin D, which in turn activate the proliferation process and / or cell differentiation[8 and 10]. In the absence of Wnt stimulation, the cytoplasmic β-catenin level is kept low through its interaction with the cadherin molecule at the intercellular adhesion sites of the plasma membrane or by degradation in the proteasome triggered by the β-catenin phosphorylation by the complex formed by GSK3β/Axina/APC. Activation of the Wnt signaling pathway leads to inhibition of GSK3β (GlycogenSynthaseKinase 3β) mediated by cytoplasmic protein Dsh (DishevelledProtein) and consequently β-catenin accumulation in the cytoplasm and nucleus[8].

Ovarian Determination

Female gonadal differentiation possibly occurs in the absence of SRY gene expression and in the expression of DAX-1 and Wnt4, which are located at 1p31-p35. Wnt4 encodes a member of the family of growth factors involved in intracellular signaling[9]. In mouse embryos it has been shown to be essential in signaling metephrenic kidney nephrogenesis, also expressing in the mesonephro, where it participates in the formation of the gonads and the Müller ducts[11]. Duplication of 1p31-p35 produces Wnt4 over expression and induces DAX1 expression and can cause sex reversal by the same mechanism as Xp21 duplication. A heterozygous mutation in the Wnt4 gene in a

patient with Mayer-Rokitansky-Kuster-Hauser syndrome characterized the absence of uterus and vagina in women with primary amenorrhea[4].

Wnt cancer

The Wnt pathway controls cellular fate during the embryonic development process. It also persists as a regulatory key for homeotase in adult self-renewing tissues, in which the mutational dysregulation of the Wnt cascade is closely associated with malignant transformation. The intestinal epithelium represents the best understood example for the closely linked roles of Wnt signaling in static homeo self-renewal and malignant transformation. Development and homeostasis in all multicellular organizations depends on a complex interaction between processes involved in proliferation, migration, differentiation, association, adherence, and death. This diverse set of general responses is largely coordinated by a small number of intercellular signals such as the BMP, TGF, Notch, Hh, and Wnt pathways. Wnt signaling drives tumorigenesis is involved in different stages of intestinal development and adult epithelial homeostasis[37 and 38].

Wnt and Glioblastoma

One of the most striking features of glioblastomas (GBMs), higher grade glioma (grade IV), is its aggressiveness and high standard care assistance, leading to a short survival period approximately 5 years after the first diagnosis[40]. Treatment failure is due to the high degree of heterogeneity of these tumors, as well as the mutation and dysregulation of various signaling pathways contribute to diffuse infiltration into the parenchyma of a normal brain[39].

The Wingless (Wnt) MMTV family of integration sites play an important role in many biological processes, starting in the early stages of development and continuing into adulthood until death. High levels of Wnts such as Wnt3a, Wnt5a, Wnt7a, Wnt5b, and Wnt2 have been associated with bacterial infections, autoimmune diseases, and neurodegenerative diseases. Humans have 19 lipid and glycosylated Wnt proteins and this signaling pathway can be divided into β-catenin-dependent and independent, both of which are important in regulating biological processes[39].

This pathway participates in cellular communication, micro modulation of the environment and the immune response is currently being studied, Wnt β-catenin signaling being aberrantly activated in gliomas, mainly GBMs, due to the accumulation of mutations and/or deregulation of certain proteins. Changes in this pathway affect signals transmitted between cells, modulating different responses, including inflammatory responses[39].

CONCLUSION

Cellular and molecular events depend on the signaling pathways that are controlled by the Wnt gene family, which participate in the formation of systems in temporal and spatial patterns and in normality and abnormality during prenatal and postnatal embryonic development.

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