Arthrogryposis

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Arthrogryposis (arth = joint; grp = curved; osis = pathological state) describes a broad range of phenotypes consisting of multiple congenital joint contractures presenting at birth. About 1 in 3000 live births presents with some form of arthrogryposis, many of which are nonprogressive and improve with physiotherapy. The core root of arthrogryposis is fetal akinesia, or lack of fetal movement, that results in contractures forming in the joints.

contracture arthrogryposis congenital

1. Introduction

Movement is required for normal joint development; it influences the structure of the joints, as well as promoting cellular signaling that guides normal tissue development. Mechanical forces also influence bone morphology, affecting organization of chondrocytes, bone elongation, and differential growth, all affecting the shape of bones as they develop. Fetal akinesia impairs joint formation, which may lead to joint fusions. Furthermore, tension is required for normal tendon development, forming a connection between bone and muscle [1]. Arrested movement during development has significant impact on the formation of the skeleton, joints, muscle, and connective tissues.

The full range of joint movement in utero can be perturbed both intrinsically and extrinsically. Intrinsically, mutations affecting the muscle, bone, connective tissue, and neural system can affect the range of movement of joints. Currently, there are over 400 genes associated with arthrogryposis broadly, encapsulating a wide diversity of genes affecting different pathways, including genes associated with axon structure, circulatory development, or synaptic transmission [2]. Extrinsically, maternal disease or exposures, uterine space limitation, and decreased blood supply are also root causes for contraction defects [3][4]. Because joint motion is affected by many different systems, a wide range of issues during development can arrest joint motion.

A subset of arthrogryposis is described as Distal Arthrogryposis (DA), a group of genetically induced contractures that predominantly affect the joints of the distal limbs, including the hands, wrists, ankles, and feet. Clinically, the lower extremity manifestations commonly include clubfoot and vertical talus. There are currently 10 classifications of DA, including Sheldon-Hall syndrome (DA2B) and Freeman-Sheldon syndrome (DA2A) [5][6][7][8]. Freeman-Sheldon syndrome is considered the most severe form of DA, and also presents with facial contractures [8].

Currently, DA patients are offered supportive care to improve quality of life, including occupational therapy, physical therapy, and surgery [9]. While these treatments improve outcome for patients, they often fall short of complete restoration of range of motion in the joints and functionality. This strategy also fails to address underlying causes

for DA, such as muscle weakness and impaired neurotransmission. Therefore, further investigation is necessary to understand the impact of disease variants which will allow us to determine the most effective treatment options for patients.

Lethal Congenital Contracture Syndromes (LCCS) are included, as some of the same genes and disease mechanisms apply to this serious condition, which is typically fetal or neonatal lethal. LCCS presents with severe generalized contractures, along with many other typical features including incomplete lung development, and polyhydramnios [10]. In contrast to DA, which is most often inherited as an autosomal dominant condition, LCCS has only been described in the autosomal recessive state. Eleven subtypes have been described to date [9].

Various disease models have been developed to examine the mechanisms behind DA and to test therapeutic interventions. Molecular and single-cell studies are useful for precisely examining the effects of DA-causing variants on the affected proteins and tissues. Access to human tissues, particularly from muscle biopsies, has facilitated molecular analysis for research, yet is clinically useful only in select cases [11][12]. In addition, protein modeling can help predict the impact of various amino acid substitutions on molecular interactions [13][14]. On the other hand, animal models are necessary to analyze the effect of single gene variants on organisms on scales larger than single cells. The effect of zygosity and gene dosage may also be better studied in animal models to assess interactions between normal and abnormal gene products. Animal models are also useful for studying experimental interventions that may improve patient quality of life and outcome, acting as stand-ins for potential human patients.

Models of human disease are rapidly becoming more sophisticated, with the ability to knock-in single nucleotide variants and create conditional (tissue specific or time-dependent) knockouts [15][16]. Loss-of-function alleles, which are often easier to generate, provide critical information about gene function, but may not fully explain autosomal dominant phenotypes in which gain-of-function or dominant negative effects can cause markedly different phenotypes. Conditional knockouts, while very helpful in defining gene function, rarely replicate the human phenotype in its entirety, but may be required when early lethality limits further study. These methods allow researchers to design models that more accurately represent these human conditions, and replicate pathogenic effects broadly or in specific tissues.

2. Lethal Congenital Contracture Syndrome

In contrast with DA, which are more common and often autosomal dominant, Lethal Congenital Contracture Syndromes (LCCSs) are a group of rare autosomal recessive forms of arthrogryposis. LCCS are characterized by lack of fetal movement (akinesia), micrognathia, incomplete lung development, polyhydramnios, characteristic contractures of the limbs (clubfoot, hyperextended knees, elbow and wrist flexion contractures) and motoneuron degeneration. Eleven subtypes of LCCS have been characterized. However, there are likely to be many more genes that result in these conditions as more genetic studies are performed on products of conception due to spontaneous abortion or stillbirth. LCCS is more common in communities with high rates of consanguinity consistent with the recessive inheritance pattern. Variable expression of LCCS phenotypes may be due to residual

gene function in patients with missense variants or modifier genes. The recessive phenotypes of LCCS have made them more amenable to study by complete knockdown of gene expression.

2.1. Nuclear mRNA Export (GLE1, ERBB3, and PIP5K1C)

The first three LCCS subtypes may all act through a similar pathway by supporting nuclear mRNA export. LCCS type 1 (LCCS1) is caused by mutations in *GLE1* RNA Export Mediator (*GLE1*), a regulator of post-transcriptional gene expression [17]. *GLE1* acts as an mRNA export factor, as well as by mediating translation initiation and termination [14]. In mice, in situ hybridization showed marked expression in the neural tube of 11 dpf embryos, specifically in the ventral portion from which motoneurons generate [17]. In zebrafish, the gene is expressed prominently in the central nervous system during development [18].

A mutation in *GLE1*, Fin_{Major}, has been linked to LCCS1 by causing a splice-site mutation that results in a 3 amino acid insertion in the coiled-coil domain [17]. The coiled-coil domain is required for the protein to self-associates to form oligomers, and one group examined the effect of the Fin_{Major} mutation on polypeptide self-association in vitro and in vivo [19]. Both in vitro and in living cells, the GLE1 protein self-aggregated, and Fin_{Major} mutant oligomers were malformed. In human cell culture and in the yeast model, these malformed oligomers were found to perturb mRNA export from the nucleus [19].

Because the Fin_{Major} mutation reduced function of the GLE1 protein in mRNA transport, *gle1* knockdown and knockouts were studied in zebrafish to understand its effects on development. Knockouts developed with small eyes and underdeveloped jaws and pectoral fins [18]. Cell death was also observed in the head and spinal cord, and there were fewer motoneurons than in wild type fish. Motoneurons also exhibit aberrant branching that worsened with age. Maternal *gle1* mRNA is loaded into the yolk sac of oocytes, where it contributes to zebrafish embryogenesis; therefore, morpholino oligonucleotides were also used to knock down expression of the mRNA in embryos. This exacerbated the phenotype, with CNS cell death becoming apparent earlier in development, at 1 dpf, which suggests an important role for *gle1* for early development. Notably, this phenotype is rescued in morphants injected with human wild type *GLE1*, but not when injected with the Fin_{Major} allele [18]. Thus, this zebrafish model may be a viable tool for screening and determining the pathogenicity of human alleles.

LCCS2 is due to loss-of-function mutations in Erb-B2 Receptor Tyrosine Kinase 3 (*ERBB3*), which encodes HER3, a known modulator of the phosphatidylinositol pathway [20]. Interestingly, variants in LCCS3 were found to be due to variants in Phosphatidylinositol-4-Phosphate 5-Kinase Type 1 (*PIP5K1C*), which encodes the enzyme PIPK-gamma of the phosphatidylinositol pathway [21]. Nouslainen et al. realized that both *ERBB3* and *PIP5K1C* are involved in the synthesis of inositol hexakisphosphate, which binds directly to yeast *Gle1*, activating *Dbp5* for mRNA transport [17]. Because Gle1 is expressed in the neural tube during development, pathogenic variants in this gene can be devastating to development of the nervous system, as *Gle1* is integral to mRNA transport [17]

2.2. Peripheral Nerve (CNTNAP1, ADGRG6, GLDN)

The genes responsible for LCCS7, LCCS9, and LCCS11 are all highly expressed in peripheral nerves and required for proper peripheral nerve function. *Contactin Associated Protein 1* (*CNTNAP1)*, which causes LCCS7, is a contactin-associated protein that is required for localization of the paranodal junction proteins contactin and neurofascin. *CNTNAP1* is also required for the normal spatial expression patterns of neuronal sodium and potassium channels [22]. Likewise, the causative gene for LCCS11, *gliomedin (GLDN)*, is a ligand for neurofascin and Nrcam, which are axonal immunoglobulin cell adhesion molecules critical for association with sodium channels at the nodes of Ranvier [23]. *Adhesion G Protein Coupled Receptor G6 (ADGRG6)*, which is also known as GPR126, is required for normal Schwann cell development. Thus, defects in all three genes likely result in similar peripheral nerve dysfunction at very early stages in development that leads to the LCCS phenotype.

3. Conclusions

Many techniques and organisms have been used for modeling arthrogryposis, each of which provides complementary information that is essential for understanding basic mechanisms and will yield translational benefits to human patients. There is an expanding list of genes that are associated with limb contractures, as one of many clinical features, beyond those discussed in this review article. Other genes are yet to be discovered, and disease models are often needed to provide evidence of causality. Furthermore, as exome sequencing becomes standard care, disease models may be helpful to facilitate variant interpretation. However, it will be essential to develop more efficient methods for introducing and studying large numbers of individual variants.

Although most genes responsible for distal arthrogryposis and LCCS are skeletal muscle sarcomeric genes or genes critical for neuronal function and neuromuscular transmission, crucial aspects remain to be established using disease models. It is important to determine whether common pathways and mechanisms supported by the genetic data will predict a unifying approach to therapy. Furthermore, now that gene therapies are becoming viable treatment mechanisms, where and when the defect needs to be corrected to prevent development of the DA or LCCS phenotype needs to be elucidated. Disease models will be essential to improve treatment for these challenging disorders.

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