Neuropathies of Stüve-Wiedemann Syndrome due to mutations in leukemia inhibitory factor receptor (LIFR) gene

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ABSTRACT

Stüve-Wiedemann syndrome (STWS; OMIM #610559) is a rare disease that results in dysfunction of the autonomic nervous system, which controls involuntary processes such as breathing rate and body temperature. In infants, this can result in respiratory distress, feeding and swallowing difficulties, and hyperthermic episodes. Individuals may sweat excessively when body temperature is not elevated. Additionally, individuals have reduced ability to feel pain and may lose reflexes such as the corneal reflex that normally causes one to blink, and the patellar reflex resulting in the knee-jerk. STWS usually results in infant mortality, yet some STWS patients survive into early adulthood. STWS is caused by a mutation in the leukemia inhibitory factor receptor (LIFR) gene, which is inherited in an autosomal-recessive pattern. Most LIFR mutations resulting in STWS cause instability of the mRNA due to frameshift mutations leading to premature stop codons, which prevent the formation of LIFR protein. STWS is managed on a symptomatic basis as no treatment is currently available.

Introduction

Stüve-Wiedemann syndrome (STWS) was first described in 1971 in two sisters with congenital bowing of the tibia and femur. While both patients experienced respiratory distress and died within a few days, one also suffered from hyperthermia1,2. Although the prognosis of STWS remains poor today, recent reports show that some STWS patients survive into adulthood3,4. STWS patients are phenotypically identical to Schwartz-Jampel syndrome type 2 (SJS2) patients5,6, and both SJS2 and STWS have been linked to a mutation of the leukemia inhibitory factor receptor (LIFR) gene on chromosome 5p13.1, and SJS2 and STWS are now considered the same syndrome7. STWS is found across multiple ethnic groups in multiple regions of the world including North America, Europe, and the Middle East7,8-12.

The skeletal features of STWS place it within the bent-bone dysplasias13, characterized by bowing of the long bones with cortical thickening and rarefaction, wide and blurred margins of the metaphyses, contracture and limited mobility of elbows and knees, osteopenia, flared iliac wings, hypoplasia of the lower ilia, and an abnormal trabecular shape13,14. Progressive bowing of the long bones, severe spinal deformities, osteoporosis and spontaneous fractures occur. Joints may be prominent with restricted mobility. While skeletal features are important, skeletal symptoms will not be the focus of this review, and we will restrict our discussion to nervous system symptoms.
Clinical manifestations

Many individuals with STWS do not survive beyond the first few months of life due to respiratory distress, difficulties with feeding and swallowing, and hyperthermic episodes1,7,9,15,17. Patients that do survive show an improvement in prognosis as a normal breathing rhythm is established and the ability to swallow is gained, yet difficulties with swallowing can still occur later in childhood9. Temperature instability is accompanied by excessive and paradoxical sweating. Other signs of dysautonomia persist, such as a smooth tongue, absent corneal and palatellar reflexes, and reduced pain sensation. Physical growth and motor development is delayed, but intelligence is normal7-9. The smooth tongue phenotype seen in STWS is due to a lack of fungiform papillae, normally found on the upper surface of the tongue. The inner structural connective tissue of fungiform papillae is highly innervated and provides the ability to distinguish taste. Taste bud development and an important symptom that is a key indicator of the role LIFR plays in normal neuronal differentiation25 and nerve cell differentiation26. Additionally, a neurologic function has been described for FYB through an association with hereditary motor-sensory neuropathy27. OSMR, like LIFR, is able to bind to glycoprotein (gp)130 to form heterodimers within the plasma membrane. OSMR has also been implicated in the respiratory system28, and the nervous system29, as well as metabolic symptoms such as mature-onset obesity, severe hepatic steatosis, and insulin resistance30.

OSMR plays a key role in bone homeostasis as demonstrated by the OSMR (-/-) mouse, which exhibits an osteopetrosic phenotype due to an effect on osteoclast differentiation31,32. The OSMR (-/-) mouse however, does not display the autonomic manifestations seen in STWS patients, suggesting that loss of OSMR by itself would not result in STWS. Therefore, the presence of OSMR within the candidate region is likely due to gene duplication and its presence within the candidate region is probably coincidence.

Proteins that play an essential role in the LIFR signaling pathway as ligands or as competing receptor, such as the cytokine receptor-like factor 1 (CRLF1), cardiotrophin-like cytokine factor 1 (CLCF1), neuropoietin (NP), and ciliary neurotrophic factor (CNTF) may play a role in the neuronal symptoms of STWS9 and are discussed in more detail.

The lifr protein and signaling

The LIFR Protein

The LIFR protein (glycoprotein-190; gp190) is composed of a signal peptide followed by three main domains. The extracellular domain (45-833aa) includes two cytokine receptor homology domains (CRH1 and CRH 2), one Ig-like domain (Ig), and one type III fibronectin domain with three modules (FNIII). The transmembrane domain (TM; 834-858aa) is located between the extracellular domain and the cytoplasmic domain (CD; 859-1097aa) (Figure 1).
The LIFR Signaling Pathway

LIFR binds with low affinity to several IL-6 cytokine family members, including leukemia inhibitory factor (LIF), oncostatin-M (OSM), ciliary neurotrophic factor (CNTF), neuropoietin (NP), and ciliary neurotrophin-like cytokine factor 1 (CLCF-1, also abbreviated as CLC)\(^{13-30}\) (Figure 2). Both LIF and OSM bind to the LIFR. LIF binds to LIFRβ, which then recruits gp130 for higher affinity and cell signaling\(^{21}\). In contrast, OSM binds gp130 with low affinity but has little to no biological activity unless a second receptor chain is recruited, either the LIFRβ or the more highly specific OSMRβ\(^{37-40}\). CT-1 binds to gp130 and LIFR, as does CLCF-1/CRLF1, NP and sCRLF1. Additionally, binding may occur in a competitive fashion with other cytokines, increasing the complexity of signaling through LIFR.

Figure 2. Cytokines interacting with LIFR. Leukemia inhibitory factor (LIF), oncostatin-M (OSM), ciliary neurotrophic factor (CNTF, neuropoietin (NP), and ciliary neurotrophin-like cytokine factor 1 (CLCF-1/CRLF1 or a soluble form sCNTFR) bind to LIFR-containing heterodimeric receptors. LIFR can associate with other receptor subunits including gp130 and CNTFR. OSM and LIF interact with LIFR in association with gp130. CT-1 associates with LIFR with gp130 and potentially other receptor subunits. CNTF interacts with LIFR in association with gp130 and CNTFR, as does CLCF-1/CRLF1, NP and sCRLF1. Additionally, binding may occur in a competitive fashion with other cytokines, increasing the complexity of signaling through LIFR.

The LIFR Signaling Pathway

LIFR binds with low affinity to several IL-6 cytokine family members, including leukemia inhibitory factor (LIF), oncostatin-M (OSM), ciliary neurotrophic factor (CNTF), neuropoietin (NP, also abbreviated as CTF2 in mouse, and CTF2P in human), and ciliary neurotrophin-like cytokine factor 1 (CLCF-1, also abbreviated as CLC)\(^{13-30}\) (Figure 2). Both LIF and OSM bind to the LIFR. LIF binds to LIFRβ, which then recruits gp130 for higher affinity and cell signaling\(^{21}\). In contrast, OSM binds gp130 with low affinity but has little to no biological activity unless a second receptor chain is recruited, either the LIFRβ or the more highly specific OSMRβ\(^{37-40}\). CT-1 binds to gp130 and LIFR, while CNTF first binds
to ciliary neurotrophic factor receptor (CNTFrs) before recruiting LIFRα23. NP signals through a receptor complex comprising CNTFRα, gp130, and LIFRα42. CNTFRα, gp130, and LIFRα promote the survival of cholinergic neurons58. Similarly, choline acetyltransferase gene expression, which in turn promotes the survival of cholinergic neurons59. CNTF enhances the differentiation and survival of motor neurons60. Therefore, the lack of LIF downstream signaling leads to the cardiovascular phenotype seen in STWS. Similarly, CT-1 is important for the cholinergic transdifferentiation of cardiac sympathetic neurons. Hence, it is likely that a lack of CT-1 downstream signaling leads to the cardiovascular phenotype seen in STWS. The reduction in motor neurons seen in STWS is due in part to the inability of LIF to signal through the mutated LIFR23. OSM is likely to be one of the LIFR ligands responsible for the respiratory distress and dysphagia seen in STWS.

### Cardiotrophin-1 (CT-1)

CT-1 plays an important role in the cholinergic transdifferentiation of cardiac sympathetic neurons in rodents59,65. Specifically, CT-1 loss reduced the number of preganglionic sympathetic neurons, which are important for inducing heart rate, ventricular pressure, and contractility66. CT-1 is also known to induce cardiac myocyte hypertrophy and vascular smooth muscle cell proliferation in vitro67. Therefore, the lack of CT-1 signaling in STWS may play a role in the cardiovascular phenotype67 and in motor neuron survival60. A role for CT-1 in airway smooth muscle cells has been identified69,70, and therefore, an absence of CT-1 signaling in STWS may contribute to the respiratory phenotype of STWS. Similarly, CT-1 is important for the cholinergic transdifferentiation of cardiac sympathetic neurons. Hence, it is likely that a lack of CT-1 downstream signaling leads to the cardiovascular phenotype seen in STWS59,61. The reduction in motor neurons seen in STWS is due in part to the inability of CT-1 to signal through the mutated LIFR23. CT-1 is likely to be responsible for the respiratory distress and dysphagia seen in STWS.

### Ciliary Neurotrophic Factor (CNTF)

STWS includes autonomic nerve dysfunction2, and ciliary neurotrophic factor receptor (CNTFR) gene has also been linked to autonomic nervous system dysfunction3,7. CNTF is expressed in the developing nervous system, particularly in the motor neurons, and it plays a role in motor neuron survival23. CNTF are known to stimulate cholinergic differentiation in sympathetic neurons, inducing choline acetyltransferase gene expression, which in turn promotes the survival of cholinergic neurons58. Similarly, LIF is important for the cholinergic transdifferentiation of cardiac sympathetic neurons. Hence, it is likely that a lack of LIF downstream signaling leads to the cardiovascular phenotype seen in STWS59,61. LIF also has neuromodulatory roles in the respiratory airways62. LIF enhances the differentiation and survival of motor neurons.

### Oncostatin-M (OSM)

OSM shares similarities with LIF, as both are able to induce the differentiation of myeloid leukemia cells to macrophage-like cells in mice63. LIF and OSM are located near each other on chromosome 22, and their arrangements suggest that LIF and OSM may be the result of a gene duplication event of an ancestral gene64.

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### Leukemia Inhibitory Factor

LIF is a pleiotropic cytokine, secreted by a variety of cell types, including epithelial and stromal cells53, osteoblasts54,55, bone marrow stromal cells, fibroblasts, astrocytes, heart myoblasts, T lymphocytes, monocytes, and thymic epithelial cells among others56. LIF acts as a neurotrophic factor57 and may play a role in motor neuron innervation49,51. LIF is known to stimulate cholinergic differentiation in sympathetic neurons, inducing choline acetyltransferase gene expression, which in turn promotes the survival of cholinergic neurons58. Similarly, LIF is important for the cholinergic transdifferentiation of cardiac sympathetic neurons. Hence, it is likely that a lack of LIF downstream signaling leads to the cardiovascular phenotype seen in STWS59,61. LIF also has neuromodulatory roles in the respiratory airways62. LIF enhances the differentiation and survival of motor neurons.

### Table 1: LIFR ligand and associated symptoms

<table>
<thead>
<tr>
<th>STWS phenotype</th>
<th>Cytokine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth tongue</td>
<td>LIF, CNTF</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>LIF, OSM, CT-1</td>
</tr>
<tr>
<td>Cardiovascular abnormalities</td>
<td>LIF, CT-1</td>
</tr>
<tr>
<td>Paradoxical sweating</td>
<td>CCLF1/CRLF1</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>CT-1?, OSM?, CCLF1/CRLF1?</td>
</tr>
<tr>
<td>Respiratory distress</td>
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</tr>
<tr>
<td>Short stature</td>
<td>CNTF</td>
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the cardiotrophin-1 gene. NP or CTF2, is predominantly expressed in mouse neuroepithelia during embryonic life, acts through a receptor complex comprising CNTFRα component, gp 130, and LIF receptor. Like CNTF, it promotes the survival of embryonic motor neurons and could increase the proliferation of neural precursor cells. Interestingly, the human gene has evolved into a pseudogene due to an 8 base pair deletion causing a disruption in the reading frame. This suggests that signaling via CNTF can compensate in the absence of a functional CTF2 in humans. While NP (CTF2) plays key roles in other mammals, it does not play a role in the symptoms of STWS.

NP is highly expressed in embryonic neuroepithelia and in the retina. NP can sustain the in vitro survival of embryonic motor neurons and could increase the proliferation of neural precursors. NP induces neuroepithelial cells to differentiate into astrocytes, and does so in coordination with bone morphogenetic protein 2 (BMP2)43,52,73.

Cardiotrophin-like Cytokine Factor-1 (CLCF-1)

Crisponi syndrome and cold-induced sweating syndrome share some features with STWS, such as feeding difficulties, trismus, paradoxical sweating (i.e., sweating with low body temperatures72), and hyperthermic episodes74. Crisponi syndrome is now considered to be the same disorder as cold-induced sweating syndrome75, and cold-induced sweating syndrome is caused by mutations in the CLCF-1 or CRLF-1 genes. CLCF-1 binds with either CRLF-1 (cytokine receptor-like factor-1) or sCNTFR (soluble ciliary neurotrophic factor receptor) and then competes with CNTF (ciliary neurotrophic factor) for the receptor complex composed of CNTFR, LIFR and gp13043,45,76. Therefore, it is likely that the dysautonomic symptoms seen in STWS are caused by a lack of CLCF-1/CRLF-1 signaling due to a mutated LIFR gene. Additionally, Crlf-1/Crfrf-1 is responsible for cholinergic differentiation of neurons innervating sweat glands77. Mice lacking Crlf-1, Cntfr and Crf-1 are unable to suckle and die shortly after birth78. These mice also have a reduced number of motor neurons in the facial nucleus79. Therefore, a lack of CLCF-1/CRLF-1 signaling leads to dysphagia and facial muscle contractions observed in STWS.

Future directions

Although most reported cases of STWS are associated with a mutation in the LIFR gene, some diagnosed cases do not have a demonstrable mutation in the LIFR gene. Although it is possible that those patients were misdiagnosed, as STWS shares many traits with other syndromes, it is also very likely that other genes play a role in STWS. Identical frameshift mutations in the LIFR gene in different individuals have also been reported to show differing outcomes or severity.

Even in the cases where LIFR signaling is known to be the root cause of STWS, connections between signaling and symptoms have not been fully elucidated. As many cytokines possess redundant roles, it is likely that there is overlap in function. Additional proteins involved in STWS will likely be discovered as additional research is carried out.

The future holds promise for potential new treatments for STWS. In the case where a single mutation causes STWS, gene editing technologies such as CRISPR/Cas9 may be used to directly modify and correct the STWS associated change in the genome80. If successful, correcting the LIFR gene could result in the expression of a normal and functional LIFR protein. Antisense mediated exon skipping may also be a useful strategy in cases where exons encode independently folding domains within the protein or where the remaining domain can still fold stably and correctly and carry out the function of the normal protein81. Exon skipping strategies may be especially applicable in cases where a mutation causes a change in reading frame, and skipping of an exon will restore the proper reading frame. Many of the identified disease causing mutations are nonsense mutations, introducing a premature stop codon within the coding regions, resulting in the production of a truncated protein or alternatively, mRNA template degradation. It may be possible to promote read-through of premature stop codons using aminoglycoside antibiotic treatment82-84 that influences the fidelity of the stop codon recognition by changing the conformation of the rRNA. 5-(fluorophenyl)-1,2,4-oxadiazolyl-benzoic acid has also been suggested to suppress nonsense mutations by read-through and is being considered for the treatment of cystic fibrosis and may also be applicable for STWS nonsense mutations85.

Conclusions

STWS is a rare bent-bone dysplasia with dysautonomic manifestations that is generally caused by the autosomal recessive inheritance of a mutated LIFR gene. The symptoms of STWS are the result of a lack of LIFR signaling, although the exact mechanisms remain unclear for most phenomena. There is currently no treatment available for STWS. Instead, symptoms are managed accordingly. The prognosis remains poor and there are many unanswered questions regarding its pathology. Therefore, further research is needed to provide a better mechanistic understanding as well as to make progress toward novel therapies that take advantage of what we do know about the targeted manipulation of specific signaling pathways.

Acknowledgement

Authors acknowledge support by Institutional Development Award (IDeA) Program from the National Institute of General Medical Sciences of the National Institutes of Health under Grants #P20GM103408 and...
P20GM109095. We also acknowledge support from The Biomolecular Research Center at Boise State, the MJ Murdock Charitable Trust; Lori and Duane Steuckle, and the Idaho State Board of Education.

References


