



CHONDROGENESIS

| | | | | | | | | | _ | | | |
|--------------------------------|------------------------------------|---|--|---|---|-----------------------------------|--|---|--|---|---|--|
| | | | | | | | | | and the second sec | CAR I | VIc | VId |
| | nt H | | anl | | Inni | mor | Ital | Laci | | | 3 •• / •• 13-18 100 | |
| | | | | | | | ILAI | Iau | | | BMP-2 | TGF-β1 |
| | | | | | | | | | | | Bone Morphogenetic Protein 2 | Factor beta 1 |
| | | | | | | | | | | | BMP-2A | ALK-1-2-5:TGF-B RURIU |
| | | | | | | VIb | VIc | VIc | VIc | TGF- β RIII; Act RIIA, RIIB | Endoglin | |
| Iolecular Weigh | nt (kDa) The | human developmental t major signaling pathway | factors listed in the tab vs involved in Developn | le include ligands and r vental Biology. The mole | non-receptor, extracellu ecules are presented in a | 8 [*] ••/•• 13-15 | 9 [*] ••/•• 13 | 10 (13-15 99) | | | | |
| tity between m | ouse & human and | color-coded according t | to family membership of | or regulatory activity. Th | ne information presente | ed was obtained | Activin A | Nodal | GDF-5 | GDF-1 | BMP-4 | TGF- β 2 |
| ime | fron repi | n standard PubMed sour resented signaling pathw | rces. Due to space const vavs and should not be o | raints, this table does no considered definitive nor | ot include all possible m r comprehensive | odulators of the | Inhibin β_A chain | Nodal | Growth Differentiation | Growth Differentiation | Bone Morphogenetic Protein 4 | Transforming Growth |
| | | 3 F | | | P | | EUF | BWL-10 | BMP-14; CDMP-1 | Vg1 | BMP-2B | |
| | V | V | V | V | V | Vla | ALK-1,-2,-4; Act RIIA,RIIB; Endoglin; TGF-β RIII | ALK-2,-4,-7; Act RIIA,RIIB | ALK-6; Act RIIA,RIIB; BMPR-II; TGF-β RIII | ALK-4,-7; Act RIIA,RIIB; Act RI; Nodal | ALK-3,-6; BMPR-II; Act RIIA; TGF-β RIII | ALK-1,-2,-5; TGF-β RII,RIII |
| | 17 40-47 | 18 • 43-46 | 19 • 42 | 20 • 44-47 | 21 [*] • 41-47 | 22 •• ¹⁸⁻²² | 2 23 [*] ••/•• ¹³⁻¹⁵ | 24 [*] • 12-18 | 25 •• ¹⁶ | 26 [*] •••/••• ¹⁸ | 27 •• ¹⁹⁻²¹ | 28 [*] ••/••• 12 |
| | Wnt-1 | Wnt-2 | Wnt-2b | Wnt-3 | Wnt-3a | GDNF | Activin B | GDF-8 | GDF-6 | GDF-3 | BMP-5 | TGF-B3 |
| | Wingless/Int-1 type Protein 1 | Wingless/Int-1 type Protein 2 | Wingless/Int-1 type Protein 2h | Wingless/Int-1 type Protein 3 | Wingless/Int-1 type Protein 3a | Glial cell-derived | Inhibin- β_{B} chain | Growth Differentiation | Growth Differentiation | Growth Differentiation | Bone Morphogenetic Protein 5 | Transforming Growth |
| inds) | Int-1 | | Wnt-13 | Tittenis | Trotein 50 | ATF | | Myostatin | BMP-13; CDMP-2 | Vgr-2 | Tittenis | Tuctor beta 5 |
| Vf | Frizzled-1,-3,-8; Ryk | Frizzled-1,-4,-5,-9 | Frizzled-4,-5,-10 | Frizzled-1,-7,-10; Ryk | Frizzled-1,-2,-4,-5,-7,-8,-10+ LRP-6; Ryk; ROR2 | GFRα-1,-2; Ret | Act RIIA,RIIB; ALK-2,-4 | Act RIIA,RIIB; proGDF-8 | ALK-3,-6; BMPR-II | ALK-4,-7; Act RIIA,RIIB | Unknown Receptor | ALK-1,-2,-5; TGF-β RII,RIII; Endoglin |
| 34 | 36 • 42-48 | 37 • 50-55 | 38 • 50-55 | 39 • 46-50 | 40 • 44-50 | 41 •• ¹³ | 42 [*] • ¹²⁻¹⁴ | 43 •• 14-15 | 44 •• ¹⁶ | 45 [*] ••/•• ¹⁶⁻¹⁷ | 46 (a) 22-24 | 47 [*] •• 70-74 |
| F-19 | Wnt-4 | Wnt-5a | Wnt-5b | Wnt-6 | Wnt-7a | Neurturin | Activin C | GDF-11 | GDF-7 | BMP-15 | BMP-6 | MIS |
| ast Growth | Wingless/Int-1 type Protein 4 | Wingless/Int-1 type Protein 5a | Wingless/Int-1 type Protein 5h | Wingless/Int-1 type Protein 6 | Wingless/Int-1 type Protein 7a | Neurturin | Inhibin- β_c chain | Growth Differentiation | Growth Differentiation | Bone Morphogenetic Protein 15 | Bone Morphogenetic Protein 6 | Müllerian Inhibiting |
| 5 (mouse) | | i locali su | | | i i i i i i i i i i i i i i i i i i i | | | BMP-11 | BMP-12; CDMP-3 | GDF-9b | Vgr-1 | АМН |
| [·] R4+Klotho β | Frizzled-6 | Frizzled-1,-2,-3,-5,-7; Glypican-3; ROR2; Frizzled-4+LRP-5; Ryk | ROR2 | Unknown Receptor | Frizzled-5+LRP-6;Frizzled-9,-10 | GFRα-2,-1; Ret | Act RIIA,RIIB | Act RIIA,RIIB; ALK-4,-5,-7 | ALK-3,-6; BMPR-II; Act RIIA | ALK-6; BMPR-II; Act RIIA | ALK-2,-3,-6; Act RIIA,RIIB; BMPR-II | ALK-2,-3,-5-,6; MIS RII |
| 22 81 | 55 • 47-50 | 56 • 38-41 82 | 57 [*] • 36 | 58 [*] • 37 | 59 [*] • 37 | 60 •• 13 | ³ / ₈ 61 [*] ●● 20 98 | 62 [*] (a) 26 and 16 96 | 63 •• 11-14 | 64 [*] ••/•• 20-22 90 | 65 [*] ••/•• ¹⁵⁻¹⁹ | 66 [*] • 28 83 |
| F-21 | Wnt-7b | Wnt-8a | Wnt-8b | Wnt-9a | Wnt-9b | Artemin | Activin E | BMP-3 | BMP-9 | GDF-9 | BMP-7 | Lefty-A |
| ast Growth ctor 21 | Wingless/Int-1 type Protein 7b | Wingless/Int-1 type Protein 8a | Wingless/Int-1 type Protein 8b | Wingless/Int-1 type Protein 9a | Wingless/Int-1 type Protein 9b | Artemin Enovin: Neublastin | Inhibin- $\beta_{\rm E}$ chain | Bone Morphogenetic Protein 3 | Bone Morphogenetic Protein 9 | Growth Differentiation Factor 9 | Bone Morphogenetic Protein 7 | Lefty-A |
| | | Wnt-8d | | Wnt-14 | Wnt-15; Wnt-14b | | | Osteogenin; BMP-3A | GDF-2 | | Op-1 | |
| r R4+Klotho β | Frizzled-1,-10 | Frizzled-1,-8,-10 | Unknown Receptor | Unknown Receptor | Unknown Receptor | GFRα-1,-3; Ret | Act RIIA, RIIB | ALK-4; Act RIIB | Act RIIA,RIIB; ALK-1,-2; BMPR-II; Endoglin | ALK-5; BMPR-II | Act RIIA,RIIB; BMPR-II; ALK-3,-6 | Cripto; Nodal |
| 32-33 | 74 [*] • 42 | 75 [*] • 43 | 76 • 48-54 | 77 * • 37-43 | 78 [*] • 14 | 79 •• ¹³⁻¹⁴ | 4 80 [*] I 18-53 | 81 •• 11-12 | 82 (11-13 | 83 [*] •• 13-15 | 84 [*] ••• 16 | 85 [*] • 28 |
| F-23 | Wnt-10a | Wnt-10b | Wnt-11 | Wnt-16b | Norrin | Persephin | Inhibin α | BMP-3b | BMP-10 | GDF-15 | BMP-8 | Lefty-B |
| ast Growth ctor 23 | Wingless/Int-1 type Protein 10a | Wingless/Int-1 type Protein 10b | Wingless/Int-1 type Protein 11 | Wingless/Int-1 type Protein 16b | Norrie Disease Protein | Persephin | Inhibin α | Bone Morphogenetic Protein 3b | Bone Morphogenetic Protein 10 | Growth Differentiation Factor 15 | Bone Morphogenetic Protein 8 | Lefty-B |
| phatonin | | Wnt-12 | | | NDF | r Jr | | GDF-10; BIP | | MIC-1;PLAB | Op-2; BMP-8b | Letty-1, DNIF-10 |
| 3c,R4+Klotho | Unknown Receptor | Frizzled-5 | Frizzled-5,-7; Ryk | Unknown Receptor | Frizzled-4 | GFRα-4; Ret | TGF-β RIII; Act RIIA | Unknown Receptor | Act RIIA,RIIB; BMPR-II; ALK-1,-3,-6 | Unknown Receptor | Unknown Receptor | Cripto; Nodal |
| | | | | | | | | | | | | |

LPM

121. Secreted, cytoplasmic, and nuclear

122. Secreted with or without LAP association

123. LTBP-2 does not associate with TGF- β ; It is integrated into the ECM and serves as an adhesion substrate

STRUCTURE KEY LIMB BUD OUTGROWTH Monomer FIRST STEP 🔍 Homodimer • Heterodimer M Single Pass Transmembrane GPI Linked s Soluble

73. Promotes phosphate excretion

75. Blocks preadipocyte differentiation

74. Molecular weight listed is the predicted value

83-88 91* 31-35 92* ²⁴⁻²⁶ **93*** ²³⁻³⁴ **94*** 130-135 33-36 **Q** MAGP-1 MAGP-2 Klotho **Klotho** β Follistatin **FGF-BP** FLRG Microfibril-associated Microfibril-associated **FGF Binding Protein** Klotho Klotho β FSH-suppressing Protein **Follistatin-related** Hedgehog Interacting Gene Protein Glycoprotein 2 Glycoprotein 1 Protein KL; Klotho- α HBp17 KLB FS MAGP-1A; MFAP-2 FSTL3; FSRP HHIP MFAP-5; MP25 FGF R1c,R2c,R3c,R4 Activin A; GDF-8,-11; BMP-4,-5,-6,-7 FGF-1,-2,-7,-10,-22 FGF R1c,R3c,R4 Shh; Dhh; Ihh Activin A; GDF-8 Notch-1; Jagged 1,2; DLL1 Notch-1; Jagged 1 * () 140-150 109* 💿 **107**^{*} • 130-140 ⁸⁰⁻⁹⁰ **110** • 111* • ²⁶ **112 ••** 113 💿 52-55 24-27 **CRIM1 CRIM2 CV-2** TSG DAN Brorin Gremlin Crossveinless-2 Chordin-like 2 **Cysteine-rich Motor Cysteine-rich Motor** Brain-specific Chordin-like Twisted Gastrulation **Differential Screening Gene** Gremlin **Neuron 2 Precursor** Neuron 1 Precursor Protein Aberrant in Neuroblastoma CRDL2; BNF-1 CRIM3; BMPER Drm, DAND2 VWC-2 CRIM KCP; Kielin DAND1; NBL1 BMP-4,-7; TGF-β2; Nodal; PDGF-B BMP-2,-4,-6,-7; Activin A; TSG BMP-2,-4; Chordin; TGF-β BMP-2,-4,-7; GDF-5 BMP-7; TGF-β1; Activin A BMP-2,-4,-5,-6 BMP-2,-6 BMP-2,-4,-7; GDF-5 180 **125**^{*} • 215-225 **126** • 105-110 ¹⁹⁰ **123**^{*} • ²¹⁰⁻²²⁰ **127**^{*} **•** 98 **128^{*} 120-200 129** 40-42 \bigcirc LTBP-1 LTBP-2 LTBP-3 LTBP-4 Vasorin Decorin Biglycan Asporin Bone Proteoglycan II **Latent TGF**-β **Binding** Latent TGF- β Binding **Latent TGF**-β **Binding** Latent TGF- β Binding Vasorin **Bone/Cartilage** Asporin Protein 2 Protein 3 Protein 1 Protein 4 **Proteoglycan** I SLIT-like 2 PG-S2; PG40 PLAP1 SLRR1A; PG-S1 TGF- β Binding Protein 1 proGDF-8; ECM proGDF-8; LAP; ECM LAP; ECM TGF-β1,2,3 **TGF-**β1; BMP-4 TGF-β1; BMP-4 BMP-2; TGF-β1 LAP; ECM ³⁴⁻³⁸ **140** • 32-36 141 • ³⁴⁻³⁸ **142**^{*} • ⁵⁰⁻⁵² **143**^{*} • **144**^{*} **• 145**^{*} • ³⁹⁻⁴¹ **146** • 42-44 sFRP-2 sFRP-1 sFRP-3 sFRP-5 WIF-1 sFRP-4 **R-Spondin 1 R-Spondin 2** Secreted Frizzled Related Secreted Frizzled Related **Secreted Frizzled Related** Secreted Frizzled Related Secreted Frizzled Related Wnt Inhibitory Factor 1 **Roof Plate-specific Roof Plate-specific** Protein 1 Protein 4 Protein 5 Spondin 2 Protein 2 Protein 3 Spondin 1 SARP2; FrzA SARP1 FrzB FrpHE; FrzB2 SARP3; FRP1B Rspo2; Cristin-2 Rspo1 Wnt-1,-4,-8; Frizzled-8 Wnt-1,-2,-3a,-5a; Wnt-1,-3a,-4,-5a Wnt-1,-3a,-8 Frizzled-1; Wnt-7a,-8 Wnt-1; LRP-6; Frizzled-5,-8; Wnt-1; LRP-6; Frizzled-8 Wnt-5a,-11 Frizzled-4,-6,-7 Kremen-1,-2 59. Molecular weight listed is the predicted valu 77. Biomarker for congenital heart defects 92. MAGP-2 induces both Notch-1 and Jagged-1 ECD release; May form a multimer with ECM proteins 108. Enhances BMP signaling 61. Antagonizes Activin A. possibly by forming Activin AE heterodime 78. Regulates angiogenesis in the ear and eye via the Wnt signaling pathway; Disulfide-linked 93. Association of FGF-BP with HSPGs weakens HSPG attachment of FGFs and promotes their release; 109. Both enhances and inhibits BMP signaling; CV-2 is proteolytically cleaved t homodimers oligomerize to form higher order structures FGF-BP enhances the mitogenic effects of FGFs a C-terminal fragment that form a disulfide-linked heterodimer 62. Acts as a BMP antagonist 80. Forms a disulfide-linked heterodimer with B subunits 94. Alternative transcript produces a secreted form. Belongs to the glycosyl hydrolase 1 fami 111. Enhances BMP binding to Chordin; Also promotes proteolysis of Chordin (to is phosphorylated: Dephosphorylated GDF-9 is inactive 83. A divergent member of the TGF- β superfamily 95. Fundamental regulator of aging and calcium/phosphorus metabolism 116. Antagonizes Nodal and BMP 130. Antagonizes BMP activity; Forms a complex with BMP and Chordin; Percent amino acid identity 145. Potentiates Wnt signaling; Blocks LRP-6 internalization by binding Kremen 65. BMP-7 prosegment and mature form associate similar to LAP:TGF-β; Forms heterodimers with BMP-2,-4, and GDF-7 117. Antagonizes Wnt and BMP activity: Mutations cause bone dysplasias 84. BMP-8A and -8B are duplicate genes with 98% amino acid precursor identity; Molecular weight listed 96. FS-315 is the serum scavenger for Activin listed is between rat & human 147. Potentiates Wht signaling: Signals independently through LRP-6 is the predicted value 131. ECM protein: Blocks/antagonizes VEGF and PDGF signaling 118. Antagonizes Wnt (by binding LRP) and BMP activity Binds to Activin/ALK-4 or to Nodal/ALK-4 to generate low efficacy, signaling receptor. 148. Molecular weight listed is the predicted value 66. 42 kDa proprecursor is bioactive; 34 kDa form is inactive; 28 kDa form is active 85. 42 kDa proprecursor is bioactive; 34 kDa form is inactive; 28 kDa form is active 119. Inhibits BMP activity; Promotes TGF-β1 activity 100. Regulates Nodal but not Activin signaling 132. Highly phosphorylated ECM protein 149. Activates the Wnt pathway 86. PDGF-D is activated extracellularly 67. PDGF-C is activated extracellularly 101. Possesses trypsin-inhibitory activity; Binds both the mature and prosegment of GDF-8 120. Intracellular form is 43 kDa; Secreted form is 70 kDa 87. Neuronal protein restricted to soma or dendrites

102. Possesses trypsin-inhibitory activity; Binds both the mature and prosegment of GDF-8

107. Binds to BMP proprecursors intracellularly and inhibits BMP activity; Soluble form is 10-15 kDa

104. Isoforms are tissue-specific and display unique BMP-binding affinities

89. Gas1 requires CDO for HH binding; Concentrates Shh on the cell surface

91. MAGP-1 induces Notch-1 ECD release; May form a multimer with ECM proteins

SP: Segmental Plate; IM: Intermediate Mesoderm; LPM: Lateral Plate Mesoderm; SE: Surface Ectoderm; ZPA: Zone of Polarizing Activity; AER: Apical Ectodermal Ridge

| 8* | • 24- | -30 68 | 99 | ۲ | 22-32 46 | 100* | • O _{TM/S} | 37-39 95 | 10 | 01* @ | 7 | 8-80 95 | 102* | ۲ | 65 89 |
|--|--|--|--|---|----------------------------------|--|---|--|--|--|----------------------|--|----------------------------------|---|--|
| Cripto Cripto CR-1; TDGF-1; CFC-2 | | | Cryptic Cryptic CFC-1 | | | TMEFF1 Tomoregulin-1 C9orf2 | | | GASP-1 GDF-associated Serum Protein 1 WFIKKNRP; WFIKKN2 | | | GASP-2 GDF-associated Serum Protein 2 WFIKKN; WFIKKN1 | | | |
| GDF-1,- Activin E | 3; Nodal; TGF-β1; B; TMEFF-1; ALK-4 | | G | DF-1; Nodal | | | Cripto-1 | | | GDF-8 | 3,-11 | | C | iDF-8,-11 | |
| 14 | @ 20- | -23 97 | 115 (| 0/00 | 34-42 67 | 116* | ۲ | 22-26 62 | 1 | 17* 🤆 |) 2 | 6-32 89 | 118* | ۲ | 29 97 |
| Prot to Da Gren | tein Related n & Cerberus nlin-2; DAND3 | | Cei c | Cerberus AND4; Cer1 | IS | Dante; Gre | COCO COCO mlin-3; Cer2 | 2; DAND5 | | SO SO Sclero | ST ST ostin | | Uterine associ WISE; SC | SAG Sensitiza ated Gen DSTDC-1; Ec | a tion- ie 1 todin |
| | BMP-2,-4 | | No | odal; BMP-4 | | N | odal; BMP-4 | | | BMP-2,-4,-6 | 6; LRP-5,-6 | 5 | BMP-2, | 4,-6,-7; LF | ₹P-6 |
| 30 * | ● ⁴²⁻ TSK | -46 84 | 131* S | ● PARC | 33-43 92 | 132* S | ● PP24 | 24 71 | 13 De | 33* ermate |) DDON | 22 92 tin | 134* CT | <mark>₿</mark> HRC | 28-30 97 |
| Tsukushi LRRC54; E2-induced gene 4 | | | Secreted Protein, Acidic, Cysteine-rich Osteonectin; BM40 | | | Secreted Phosphoprotein 24 Secreted Phosphoprotein 2 | | | Dermatopontin TRAMP; EQ-1 | | | Collagen Triple Helix Repeat- containing Protein 1 NMTC1 | | | |
| BMP-4,- N | -7; Chordin; DLL1; odal; FGF-8 | | PDGF TG | -AB; PDGF-B iF-β; FGF-2 | B; | | BMP-2 | | | Decorin; TGF | -β; BMP-2 | 2 | Frizzlec Wn | l-3,-5,-6; R(t-3a,-5a,-11 | OR2; 1 |
| 47* -Sp Roof S | Ondin Plate-specific pondin 3 po3; Cristin-1 | 43 90 3 | 148* R-Sp Roof I S | Ondi Plate-spec pondin 4 io4; Cristin-4 | 22 84 n 4 ific | 149* My | OCII Myocilin TIGR | 55-66 82 | 1. K | 50* (rem (ringle-co larking Ey Krm | ding Ger e & Nose | 50 92 1 ne e 1 | 151 Kre Kringle Marking | •-coding (g Eye & N Krm-2 | 56-58 89 1-2 Gene ose 2 |
| Wnt-1; | LRP-6; Frizzled-8 | | Unkn | own Recepto | or | Frizzled- | 1,-7,-10; sFF WIF-1 | RP-1,-3; | | Dkk-1,-2; | LRP-5,-6 | | D | kk-1,-2,-4 | |
| generate an N- a promote BMP act | 124. Secretion and 125. Incorpora 127. Secreted p tivity) 128. Secreted r | is depende ited into the proteoglyca | nt upon covalent asso e ECM in (SLRP) in (SLRP): Antagonize | ociation with LAP; LTBP so or potentiates TGF-B | -3 has low associa signaling. | ition with the ECM | 137. Acts intrace 142. Acts as a cir 143. Molecular v 144. The WIE doi | Ilularly to promote culating phosphoni veight listed is the p main interacts with | Wnt-media n (promote predicted v | ated signaling es phosphate excretion alue cid adduct on Wots |) with FGF-23 | | © | 2009 R&D S | ystems, Inc. |

133. ECM protein; Forms a complex with Decorin and TGF- β , increasing TGF- β activity 134. Inhibits TGF- β signaling and enhances the interaction of Wnt:ROR2 complexes 136. Antagonizes Wnt signaling when bound to Kremen-2, ; Without Kremen-2, activates LRP-6

and Wnt signaling

150. At high levels of LRP-5/6, Kremen-1 collaborates with Dkk-1 to antagonize Wnt signaling; In the absence of Dkk-1, Kremen-1 maintains LRP-6 on the cell surface