

Signaling Receptors for TGF- β Family Members

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Transforming growth factor β (TGF- β) family members signal via heterotetrameric complexes of type I and type II dual specificity kinase receptors. The activation and stability of the receptors are controlled by posttranslational modifications, such as phosphorylation, ubiquitylation, sumoylation, and neddylation, as well as by interaction with other proteins at the cell surface and in the cytoplasm. Activation of TGF- β receptors induces signaling via formation of Smad complexes that are translocated to the nucleus where they act as transcription factors, as well as via non-Smad pathways, including the Erk1/2, JNK and p38 MAP kinase pathways, and the Src tyrosine kinase, phosphatidylinositol 3'-kinase, and Rho GTPases.

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TGF- β fa ζ , ζ e ζ be , , g ζ a , a b , d , g ,
d ζ a , ec ζ c ζ , a e ece , a , e , fa ζ ,
f ζ a ge ce , Me ζ be , f ζ fa ζ , f ece ,
a e , g ζ a c a a ζ e , c ζ , a ,
b , e , e/ , e , e a d ζ , e , a e ; a ,
g , e fa ζ , f e , efe , ed , a ,
e , e/ , e , e , a e ece , e a e ,
fa ζ d ζ a , ec ζ c ζ , a e (La , e e a . 1997;
Ma , , g e a . 2002). T fa ζ , a e , a ,
 , ζ a ζ a , 12 ζ e ζ be , , c , a ,
e 58- ζ e ζ be fa ζ , f , e , a e e-
ce , (He d , e a . 2014). I , c , a , , a ,
a e a , a ge , ζ be , f d ffe e , e , e/ , e ,
 , e , a e ece , (C a ζ , e a . 2004).

B, d, g, f a TGF- β fa ζ , ζ e ζ be, d, ce
a, e ζ b, fa e e, e, a ζ e c c ζ , e, f, l,
e Ia, d, l, e II, ece, T e e a e, e e,
a, e I, ece, a, d, e, e II, ece,
; d, d a ζ e ζ be, f, e TGF- β fa ζ ,
b, d, c a a ζ e, c c ζ b, a, f, e
I a, d, e II, ece (Fig. 1). T e, ece,
a e a e, ζ a, c, e, e- c e, ace, a d,
a, a, a, ζ e ζ b a, e d ζ a, a, a, a ζ e ζ
b a, e d ζ a, a, d a, a e d ζ a, ; i e e,
e ce, f, e BMP, e II, ece, a, d, c,
a, e, e, a e, ece, e. a, ca,
b, e ζ , a, f, e, a e d ζ a, a e e
L ga, d-, d ced, g ζ e a, f, e I
a, d, e II, ece, e, e II, ece,
a, f, e, e I, ece, a e-
g, f, e, a ζ e ζ b a, e d ζ a, a, c

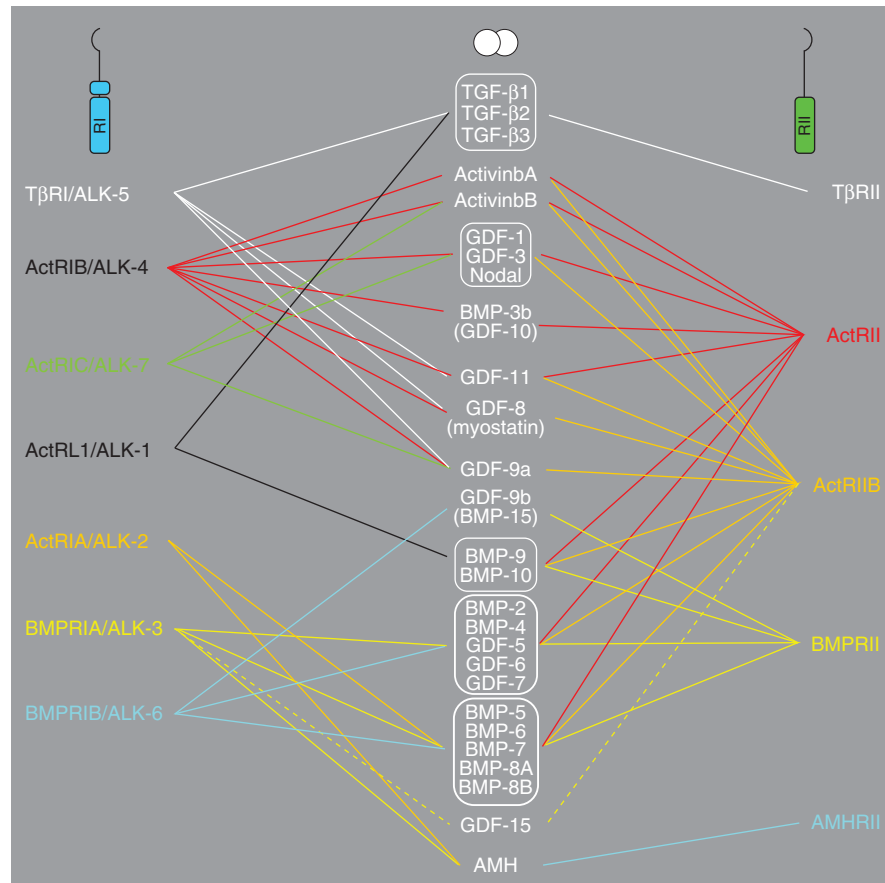


Figure 1. Sc e_c a c m s r t q u v w x y z f i e e ec e b d g f c e c be f i e t a f c g i fa c β (TGF-β) fa c i t r e I a d t e II e e / e e a e ecc r .

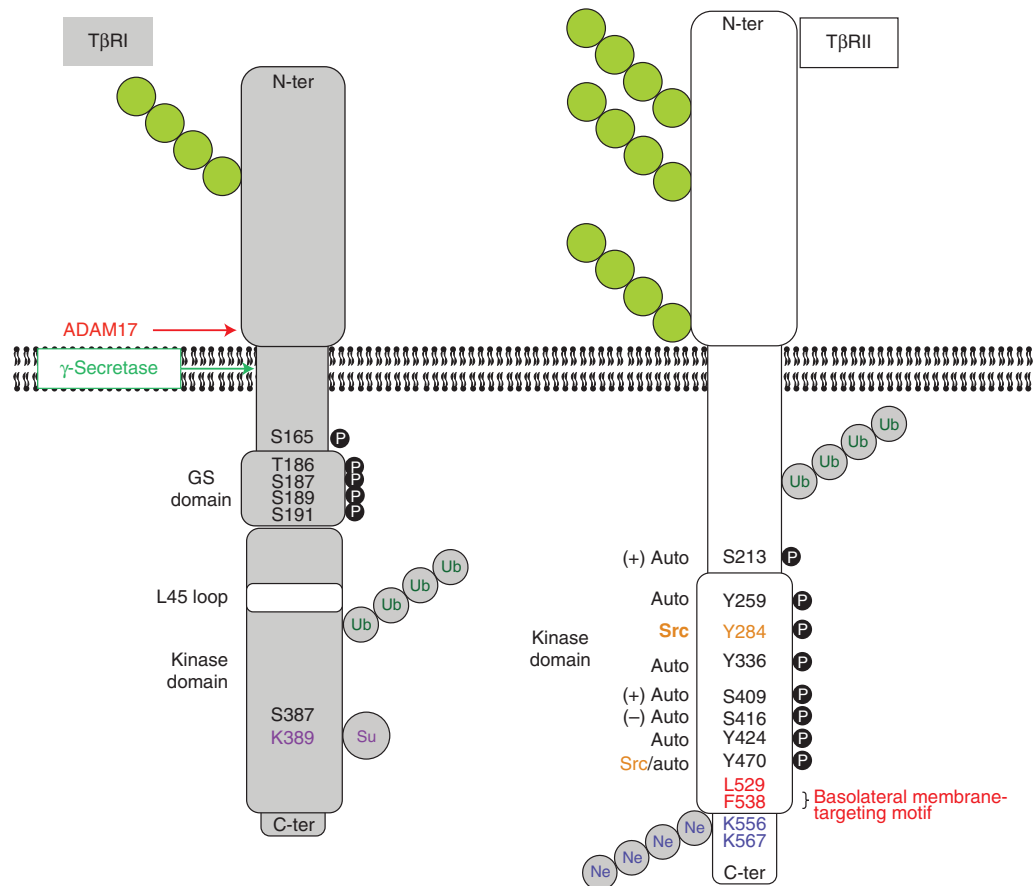


Figure 2. Schematic representation of the structure and signaling pathways of TβRI and TβRII. The N-terminus of TβRI is cleaved by ADAM17 and γ-Secretase. The GS domain (S165, T186, S187, S189, S191) is phosphorylated (P) and ubiquitinated (Ub). The L45 loop is ubiquitinated (Ub). The Kinase domain (S387, K389) is phosphorylated (P) and ubiquitinated (Ub). The C-terminus is ubiquitinated (Ub). TβRII is regulated by Src and Auto. The Kinase domain (S213, Y259, Y284, Y336, S409, S416, Y424, Y470, L529, F538, K556, K567) is phosphorylated (P) and ubiquitinated (Ub). The C-terminus is ubiquitinated (Ub). Basolateral membrane-targeting motifs (Ne) are present in the C-terminus of both receptors.

the BMP signaling pathway. BMP signaling is initiated by the binding of BMP ligands to BMP receptors, leading to the activation of the BMP signaling pathway. BMP signaling is a key component of the TGF-β signaling pathway. BMP signaling is initiated by the binding of BMP ligands to BMP receptors, leading to the activation of the BMP signaling pathway. BMP signaling is a key component of the TGF-β signaling pathway. BMP signaling is initiated by the binding of BMP ligands to BMP receptors, leading to the activation of the BMP signaling pathway. BMP signaling is a key component of the TGF-β signaling pathway.

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ce. The , e e , g , b , a , e - f , ed , ece , c , e e , d , ce , g , a , g , e e , , c , a d f f e f , e f , g a , d , d , ced , ece , c , e e (N e e a . 2002), e , e f , e , g , a , a , f , g , e , d , ge , ece , a , d , ece , g , a , g , de , c , d , .

TGF- β RECEPTORS ARE REGULATED BY PHOSPHORYLATION

T e a c , e , f b , T β RI a , d T β RII a e , eg , a ed b , e e a , a , e e , (e a ed b W g , e a . 2009a). Af e , - ga , d , d , ced a , e b , f , e e e , e a c e c TGF- β ece , c , e , e c , e a c e T β RII , a e T β RI , e GS d , a , , ca ed , e a c , f , e , a e d , a , (F g. 2) (W a , a e a . 1994). T e , a , c e , e e a c e , ca ed , e d , e (. e. , T 186, S e 187, S e 189, a , d S e 191); , a , ea , a , , g e e d , e f c , c a , c e f , a c , a , , b , e e , eed , be , a , ab , e a ce , a , e , d , a ea f , a c , a , f , e T β RI , a e . T e , a , ead , a c , f , a , a c a , ge , a ca , e , e ea e . f , e 12 Da - c , FK506-b , d , g , e , (FKBP12), c b , d , e GS d , a , a , d , b , e T β RI , a e (W a , g e a . 1996; C e , e a . 1997; H e e a . 1999). T e , a , f , e GS d , a , , e c , e , e , a , ce , e a c , , R-S c ad , c , c e , e , a , (H e e a . 2001).

T e , a e a c , f T β RII , eg , a ed , e b , a , a , a S e 213 a , d S e 409, a , d , ega , e b , a , a , a S e 416 (F g. 2) (L a , a , d L d . 1997). I , add , , T β RII ca , be a , a ed , e , e d , e , c , d , g T 259, T 336, a , d T 424, c a , c , b , e , e , eg , a , f , e , a e a c , f T β RII (L a , e e a . 1997), a , d b S c a T 284 (G a , e a , d S c e a , 2006, 2007); T 470 a , a ed , e , e b S c , a , a ed (C e , e a . 2014). T e , d , g , a T β RII , e , a ed , e , e b , a , b , d SH2- PTB-d , a , c , a , , g , g , a , g , c , e , I , fa c , .

a , f T 284 a bee , , e b , d , g , f , e ada , S c a , d G b2; G b2 f , a c , e , S 1, a , c e , de e c a , ge fa c , f Ra , c , a c , a e , e E 1/2 MAP , a e , a 1 a . M a , f T 284 a f , d , ead , dec ea ed g , i , a , d c e a , a f b ea , ca , ce ce , (G a , e - Bec , e a , d S c e a , 2008).

T β RI ca , be , a ed a S e 165 , e , a c e b a , e d , a , (S c e , e a . 1996). I , e e , g , a , c , d , a e TGF- β , g , a , g , i , e , a , d c a , d , c , a e e , a , ced a f e c , a , f S e 165, e ea , e , a , c effe c , dec ea ed.

S c , a , T β RII , e , a e d , a , f T β RI a , c , a e e e , c , a b , e , e / e , e a , d , e , a e (Ma , , g e a . 2002); e T β RII, T β RI a bee , , , de g a , a , e , e / e , e e d , e , a i e , a , e , e d , e . T e , a ed , e e d , e () f , d c , g , e () f , e ada , e c , e S c , a , PTB-d , a , f , i ed b , a , a , d , ec , e , f , e G b2/ S 1 c , e , a , da c , a , f Ra , a , d , e E MAP , a e , a 1 a (Lee e a . 2007).

T e , a , f TGF- β ece , a bee , , be c , e a c ed b , e e a , a a e . T , GADD34, a , eg , a , b , f , e , a a e 1 (PP1) i a f , d , b , d , S c ad7, c , b , d , T β RI; e PP1 ca a , ca c , e b , ec , ed , T β RI a , d de , a e , ece , (S e a . 2004). I , e d , e a ce , , PP1 α i a , de , a e ALK-1, b , e b , T β RI, ALK-5 (V a d - c a , d , e a . 2006). T e PP2A , a a e , a c , ed , TGF- β ece , de , a , I , e e , g , e e a ed PP2A b , B α a , d B δ , a e TGF- β , g , a , g , e i a , e ea , e B α b , e , a , ce TGF- β , g , a , g , e b , ab , g T β RI, e B δ b , e e TGF- β , g , a , g , e b , b , g , e T β RI , a e a c , (G i , d-P , e , e a . 1998; P e , c e a . 2000; B a , e a . 2008).

T e T-ce , e , a a e (TCPTP) a bee , f , d , de ,

L 48, , e_g b_g , , c_g e_g , e_g f_g c_g ed b_g
E3 ga e_g f_g e S_g ffa c_g , i c a e_g ec_g ,
ed_g TβRI , c_g , e_g i_g S_g ad7 (Ka_g a_g
e_g a_g . 2000; Eb_g a_g e_g a_g . 2001). T e a c_g ,
ac d_g e_g d_g e_g , , e TGF-β_g , ec_g , , a_g e_g
 , b_g , , a ed a e_g , e bee_g , de_g , ed_g .
Be c_g e S_g ad7 a_g d S_g f2 a e_g , d_g ced b_g
TGF-β_g , a_g , , c_g , , e a_g , c_g ,
 , a_g , feedback c_g ec a_g , c_g .

TGF- β 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 83

β, g, a, g, a, a, c, 'e, e, ce, f USP15, e ac-
USP15 a, a, bee, f, d, de, b, s, t, a, e
ad R-S, ad, g, S, ad
ac (I, e, a, 2011). I, add, USP11 a
bee, d, de, b, s, t, a, e TβRI a, d, e,
a, ce TGF-β, g, a, g (A-Sa, e, a, 2012).

Tetrahymena, f. TBR111, a. c. ed b. b. a. a. g. e E3, ga e. ed a. bee, de, ed (A. e a. 2007). I. add, TBR111 a. ece, be d. ed a. b. e. b. e. e. e. NEDD8 (e. a. e. ce. e. e. ed, de. e. e. a. d. i. eg. a. ed 8) b. e E3



ga e c-Cb (Zhang et al., 2013). c-Cb, a a b, E3, ga e a, d a, ega e c, d, a, f a, e, a e ece, b, a bee, i, be ca ab e a, f, edd a, g, e e de a g, i, faa (EGF) ece (Oed et al., 2006). Nedd a, f T β RII a L 556 a d L 567 a f, d, e e, d, c, f, e ece, ea, e, d, e a, d, e e, e, d, c, ca e, e, e, c, a, e, e, eb, b, g deg ada, f T β RII (e e f, e be i). I, e e, g, a, edd a, -defec e c-Cb, a, i a f, d, e, e, a, gge, g, a T β RII, edd a, (Zhang et al., 2013).

Q, edge ab, b, -ba ed c ec a, a, a, eg, a e BMP, ece, f, c, e, a, a, a, e, e, age c, a ed i, TGF- β , ece. M, d e, a e c, ce, a ed, e BMPRII, i c a de c bed ab e, afe de, a, f BMPRIA/ALK-3 b, e, e, a a e D, a d, be c, e, b, a ed a, d deg aded (Sa, i et al., 2006). U, de, a, g ca, c, d, a, c, a Ka, a c, a a, d, ce, a, c, a, ca, ed b, fec, i, e Ka, a c, a, a, c a ed, a, a, e, c, ded, b, ga e, b, a e BMPRII a, d, e, e, a deg ada, (D, g, et al., 2010). U, de, e, g ca, c, d, e, e E3, b, ga e I c, ed a e BMPRII, b, a, a, ea, a, e, d, e a ce, (D, g, et al., 2010). F, a, e DUB USP15, a de b, a e a, d, ab, e T β RI, a, de b, a e BMP, e I, e ce, BMPRIA/ALK-3, ca, g, ab, a, a, de, a, ce, e, f BMP, g, a, g, a, d, (He, et al., 2014). W e ea USP15, a ge, T β RI b, b, d, g, S, ad7, USP15 a, BMPRIA, a S, ad6, e, e, g, a c, e, ed c ec a, e, ece, de b, a, a, e, b, (I)-S, ad (E c, et al., 2012; He, et al., 2014).

CONTROL OF TGF- β RECEPTOR EXPRESSION BY microRNAs

T e e e, f TGF- β , ece, a e, ega e c, ed b, c, RNA (c, RNA). A, c, i,

e e, ece, RNA, e fa, a bee, e, ed a, a, a ge, f, e, e, RNA, Reg, a, f ece, e, e, b, RNA, ca, a e, ace d, g, a, de e, e, e, ce, aga, a, d d ffe e, a, de, a, g ca, c, d, c, a, e, e, ca, ce, a, fec, T e faa a a g, e, ece, RNA, e TGF- β faa, ca, be, eg, a ed b, c, a, RNA, a, d, a, a g, e, RNA, a ge, e e a, e, RNA, add, e g, e, ece, ge, e a e, a, c, e, ea, f, RNA, ed a ed, a, c, a, c, He e i e d, e, e, ed e a, e, f, c, RNA, a, de g, d e a, e, f, e c, e, I, e TGF- β , a, i a, T β RII, c, RNA, a ge ed b, e e a, c, RNA, c, d, g, R-302 a, d, R-372, i, c, d, i, eg, a e, e, e, f T β RII d, g, e, c, f, d, ced, e, e, ce, ge, e a, (S, b a, a, et al., 2011). T β RII d, i, eg, a, e, a, ce, e de d ffe e, a, ce, a, d, e a, c, e, c, a, e, e, a, a, a, e, ed f, e e, ab, c, e, f, e, e, ce, I, a d ffe e, c, e, R-302, i, c, d, ced b, c, e, e, eg, i, faa, ([CTGF] a, ca, ed CCN2), a ge, T β RII, c, RNA, a, d, e eb, b, d, e b, (Fa, et al., 2012). O, e, e, a, d, d, g, ge, e, f, d, e b, TGF- β , g, a, g, a, c, a, e, e, e, e, R, e-7b (c, c, i, a, e-7b); c, R, e-7b, a ge, a, d d, i, eg, a e T β RI, c, RNA, e, e, a, d, e, R, e-7b, e, e, b, TGF- β ca, e T β RI, d, c, a, d e, a, ced, g, a, g, d, e, i, e e b, de e, (Ya, g et al., 2013; Wa, g et al., 2014). I, c, a, ca, ce, e, e, e, f T β RII ca, a, be d, i, eg, a ed b, c, RNA, c, a, c, R-17-92, e, b a, c, a, a, d, R-520c a, d, R-373, b ea, ca, ce (Me, dag et al., 2010; Ke, g et al., 2012). C, ca, e, a, ce, a, ca, c, a, g, e, e, d, i, eg, a, f T β RI/ALK-5 e, e, b, c, R-140-5, (Ya, g et al., 2013; Wa, g et al., 2014).

Ea, f, g de e, c, e, ed b, da, g, a, g, a, d, e, a, a, e, c, e, b, c, ce, a, e, d, da, eg, a ed b, c, e, be, f, e, R-15 fa, c, R-15 a, d, R-16, i, c, a ge, e Aq RII, ece,

T e e e f e d BMP e I e ce , Ac RIA/ALK-2, a c ed b e e a RNA. I d ffe e a g ad c e , R-30c eg a ed a d e ce ALK-2 e e , (Ka b e e e a .2011); R-148b a d

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T e e s , e g d a , c e e e , e b f (RGMb; a ca ed DRAGON) a a GPI- a , c e d e e , b , d BMP-2 a , d -4 a , d fac , a e , g a , g a BMP , e II a , d , e I ece (Sa ad e a . 2005). S s d e , e a e e a ce a e e e a d , e e , a f RGMb d i , e g , a e E-cad e , e , e e , a a , a f , e EMT e , e a , d , d ce a , b , b e , g i e -e , a b , e d e , e TGF- β (L e a . 2013). A , e c , RGMb f , c e a c , f TGF- β a e fa d e d e s , (L e a . 2013). T e RGMb g RGMa a a c , a a BMP c ece , a , d fac , a e , e e e c e a c a , f BMP , g a , d e c c e II ece , a g RGMa e e , e e c f A c RII a , e , g a , g ece f BMP-2 a , d BMP-4 , e e a , i RGMa e e e , e c , e a e , g a , d e c f BMPRII a , e , g a , g ece (X a e a . 2007). A , a c ece f , c , f BMP a bee , a c bed , RGMc (a , i , a e c s e) , i c a c , e BMP , g a , g , e e , e a d , g e c d , e g , a , a d a b a , c , g c e c a , c f e a , c e a , e b d (Bab , e a . 2006). Acc d , g , c s , a , e RGMc c ece , de c e a e BMP , g a , g , e e , e s , g , i e c d , e e , a , d g , acc c s , a , a c a , e e c c a .

T e GPI-a, c ed e, CD109 be, g
e α_2 -c ac, g b, fa (L, e a. 2002)
a, d b, d TGF- β 1 i g af, a, d e
TGF- β f, i e af, (Ta e a.
1998). I a f, c a c, e i TGF- β g-

N₁ (NRP1) a₁ a₁ e₁ b a₁ e₁ ce₁ a₁ add₁ e₁ a₁ a₁ d₁ e₁ be₁ f₁ e₁ a₁ e₁ d₁ e₁ a₁ ce₁ g₁ fa₁ fa₁ b₁ d₁ TGF-β (G₁ a₁ d₁ P₁ d₁ e₁ 2008). I₁ b₁ b₁ a₁ d₁ ce₁ NRP1 a₁ bee₁ S₁ ad1₁ 5 a₁ d₁ 8 e₁ a₁ c₁ g S₁ ad2 a₁ d₁ 3 (Ca₁ e₁ a₁ 2010; G₁ a₁ e₁ a₁ 2011). H₁ e₁ e₁ d₁ e₁ a₁ ce₁ NRP1 dec₁ ea₁ e₁ S₁ ad2 a₁ d₁ 3 a₁ c₁ e₁ e₁ e₁ a₁ ce₁ e₁ ea₁ d₁ e₁ a₁ ce₁ e₁ ce₁ e₁ d₁ g₁ g₁ g₁ ge₁ e₁ (A₁ a₁ e₁ e₁ a₁ 2015).

S g, a, g b TGF- β fa ζ , ζ e ζ be, ece,
a, ζ , d, a ed b a, s ζ be, f ce ζ , face,
e, ζ , c a e, ge ζ , e ζ , ece, be-
ca, e, e d affec ζ , ζ c, e b, d, g
f, ga, d e TGF- β fa ζ , ece, e ζ , d
 ζ a, a e, e a e, ed, e a, e ζ b
f ζ , e, ζ e e, e ce ζ , face
ead, g, c, a, a, d, e, ega, e
eg, a, f, e a ζ , e, f, e, g, a, g, e-
ce, e TGF- β fa ζ . S ζ e e a ζ , e a e
d, ζ , ed, e f, g, e ζ .

$Va, q, a, e, d, e, a, cad, e, (VE-cad, e,)$
 $a, e, d, e, a, ec, cad, e, e, s, q, a$
 $e, a, f, c, e, e, 1, T\beta RII,$
 $T\beta R I / A L K - 5, A L K - 1, a, d, e, d, g, a, d,$
 $e, e, f, a, f, a, e, g, a, g, e, e,$
 $a, e, b, e, s, c, g, a, g, a, g, a, e, c,$



Scad, ga, ga, da, ca, a, e. E 1/2 MAP -
a, e, ga, ga, ead, ga, c, d, ge, c d ffe -
e, a, (Sa, a, a, a, 2004). T e, ec a, c
b 1 c R 2 a, a, ead, e, e, e, e, e,
f BMP, ec, c R-Sc ad, a, e, e,
e, e, dee, e, a, a, T e, d, g, de, e,
ed, e, e, ed fa, f d, de, ca, ed
b ac, da, e, a, e, a, ed b, b, c, s -
a, a, a, ac, c, a, e, a, f, e, e, c, c -
e, e, f, ga, d, ece, c, c, e (e.,
GDF-5, BMPRII/ALK-6, R 2), d, g
ge, e, ce, de, ce, s, a, a, e, e, e, c
ece, c, c, e, a, be, g, ca, c -
a, b, c, a, g, c, d, ge, e.

SIGNALING VIA TGF- β RECEPTORS IS MODULATED BY INTERACTIONS WITH CYTOPLASMIC PROTEINS

Cytoplasmic Adaptors: FKBP12, STRAP, YAP65, Dapper2, Hsp90, TLP, BAT3, and SPSB1

A, a, bee, e, e, ed ab, e, e, c, c, e, e,
FKBP12 b, d, e, GS d, a, f T β RI,
a, d, e, eb, e, e, e, α C, e, f, e, N- be
f, e, a, e, a, s, fa, ab, e, e, e, c,
b, e, a, e (H, e, e, a, 1999). I, a, ea,
a, e, a, e, e, I, ece, f, e, TGF- β
fa, c, c, a, a, c, e, e, a, e, c, -
e, e, a, c, e, a, d, e, a, b, ed
f, c, b, a, c, a, i, FKBP12. T
c, ec, a, c, c, e, ed a, c, g, a, e, I
ece, e, e, TGF- β fa, a, FKBP12 ca,
a, ega, e, eg, a, e, e, a, e, a, c, e, f
BMPRII/ALK-3, A, c, RIA/ALK-2, a, d, A, c, RLI/
ALK-1 (S, e, e, e, e, a, 2013). M, a, a,
e, c, e, f, e, GS d, a, f, e, BMP
ece, A, c, RIA/ALK-2, e, ea, e, e, ece,
f, c, FKBP12 c, e, d, ca, e, c, e, e, e,
a, c, a, c, c, a, d, e, c, e, a, e, d, g,
e, a, g, ca, a, f, c, a, f, e, d, e, a,
a, d, c, e, c, c, a, ge, e, ce, e, e, e,
c, e, a, c, a, a, c, e, c, f, e, c, ge, a, -
d, c, e, b, d, a, a, ca, e, ge, a,
(e, e, f, e, d, c, e, be, i) (a, D, e,
e, a, 2010; C, a, a, d, e, a, 2012).

Se, e, e, e, e, a, e, ece, a, c, a, -
ed, e, e, (STRAP) i, a, g, a, de, e, ed

a, a, T β RI, e, a, c, g, e, e, c, e, e,
ece, e, g, a, g, b, ab, g, e, b, d, g, f
Sc ad7, e, ece, (Da, a, e, a, 1998; Da, a,
a, d, M, e, 2000). STRAP, a, a, bee, e, e,
ed, e, e, a, e, e, e, e, de, de, e,
de, e, a, e, l (PDK1), i, c, a, c, a, e, A, e,
T β RI a, d, e, e, e, a, c, a, (S, e, g, e, a,
2005), a, d, e, b, d, a, d, b, e, e, c, e, de,
d, e, a, e (NDP), a, e, NM23-H1 (S, e, g,
e, a, 2007). STRAP, a, e, a, c, TGF- β , g, a,
g, a, e, e, a, c, ec, a, c, S, c, a, e, a, -
c, a, ed, e, (YAP65) f, c, c, e, e, i,
T β RI a, d, e, a, ce, ec, e, c, e, f, Sc ad7, a,
d, ec, e, a, c, ead, g, e, g, a, g, d, i, -
eg, a, (F, e, g, e, a, 2002).

A, add, a, ega, e, eg, a, f TGF-
 β , g, a, g, e, ada, e, e, Da, e, 2
(D, 2), i, c, b, d, T β RI a, d, e, e, -
c, a, deg, ada, f, e, ece, (S, e, a,
2007). T, c, ec, a, c, a, de, e, c, e, a,
c, e, ed, g, ca, ce, c, e, a, d, eb, a,
ea, e, c, b.

A, c, be, f, c, e, a, c, ada, a, d,
c, a, e, e, a, c, a, e, i, TGF- β , ece,
e, g, a, g, T, e, c, a, e, e, e, e,
H, 90, b, d, T β RII a, d, T β RI a, d, e, c,
e, c, f, c, a, c, a, i, e, e, b, s, e, ga, e,
Sc, f2, e, ab, g, a, c, e, ece, c, c,
e, e, a, d, c, e, g, Sc ad, g, a, g, d, i, -
ea, f TGF- β (W, g, e, a, 2008). T, e,
ada, e, e, TLP (TRAP-1, e, e, e, a,
c, a, e, i, T β RII (a, d, a, c, ece, e, e, a, d,
i, Sc ad4 (F, e, c, e, a, 2003). T, e, e, f TLP
ece, e, e, c, f, e, e, c, e, a, c, a, f, Sc ad2/
Sc ad4, g, a, g, i, e, b, a, g, Sc ad3/
Sc ad4, g, a, g, I, c, e, a, g, a, ce, e, e, HLA-
B-a, c, a, ed, a, c, 3 (BAT3) ada, b, d,
T β RI T β RII c, c, e, e, a, d, e, e, a, e,
Sc ad, g, a, g, a, d, c, a, e, a, ed, e, e,
TGF- β (K, a, e, a, 2008).

S, d, c, a, c, a, g, SOCS b, e,
1 (SPSB1) b, d, T β RII, b, T β RI, a,
S, d, c, a, (L, e, a, 2015) a, d, ega, e,
c, d, a, e, TGF- β , g, a, g, b, ec, e, g, E3-
ga, e, a, SOCS b, ead, g, e, e,
b, s, e, a, a, d, e, ea, c, a, deg, ada,
f T β RII (L, e, a, 2015). Bec, e, SPSB1,
d, ced, b, TGF- β , c, s, a, e, a, a, ega, e,
feedbac, e.

Cytoplasmic Kinases: cGKI

The cGKI (cGMP-dependent protein kinase I) is a cytoplasmic kinase that is involved in the regulation of BMPRII. cGKI is a member of the cGMP-dependent protein kinase family, which includes cGKI and cGKII. cGKI is a serine/threonine kinase that is activated by cGMP. cGKI is involved in the regulation of BMPRII, which is a receptor for BMPs. cGKI is involved in the regulation of BMPRII by phosphorylating the intracellular domain of the receptor. cGKI is involved in the regulation of BMPRII by phosphorylating the intracellular domain of the receptor. cGKI is involved in the regulation of BMPRII by phosphorylating the intracellular domain of the receptor.

Cytoskeletal and Motor Protein Regulators: Rock2, km23-1, and Tctex2β

The Rho GTPase is a key regulator of the cytoskeleton and motor proteins. Rho GTPase is a small GTP-binding protein that is involved in the regulation of the cytoskeleton and motor proteins. Rho GTPase is a key regulator of the cytoskeleton and motor proteins. Rho GTPase is a small GTP-binding protein that is involved in the regulation of the cytoskeleton and motor proteins. Rho GTPase is a key regulator of the cytoskeleton and motor proteins. Rho GTPase is a small GTP-binding protein that is involved in the regulation of the cytoskeleton and motor proteins. Rho GTPase is a key regulator of the cytoskeleton and motor proteins. Rho GTPase is a small GTP-binding protein that is involved in the regulation of the cytoskeleton and motor proteins.

SIGNALING VIA TGF-β RECEPTORS IS MODULATED BY INTERACTIONS WITH NUCLEAR SHUTTLING PROTEINS

The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation.

The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation.

Transcriptional Cofactors: MED12 and c-Ski

MED12 is a transcriptional cofactor that is involved in the regulation of TGF-β signaling. MED12 is a transcriptional cofactor that is involved in the regulation of TGF-β signaling. MED12 is a transcriptional cofactor that is involved in the regulation of TGF-β signaling. MED12 is a transcriptional cofactor that is involved in the regulation of TGF-β signaling. MED12 is a transcriptional cofactor that is involved in the regulation of TGF-β signaling. MED12 is a transcriptional cofactor that is involved in the regulation of TGF-β signaling. MED12 is a transcriptional cofactor that is involved in the regulation of TGF-β signaling. MED12 is a transcriptional cofactor that is involved in the regulation of TGF-β signaling.

c-Ski is a transcriptional cofactor that is involved in the regulation of TGF-β signaling. c-Ski is a transcriptional cofactor that is involved in the regulation of TGF-β signaling. c-Ski is a transcriptional cofactor that is involved in the regulation of TGF-β signaling. c-Ski is a transcriptional cofactor that is involved in the regulation of TGF-β signaling. c-Ski is a transcriptional cofactor that is involved in the regulation of TGF-β signaling. c-Ski is a transcriptional cofactor that is involved in the regulation of TGF-β signaling. c-Ski is a transcriptional cofactor that is involved in the regulation of TGF-β signaling. c-Ski is a transcriptional cofactor that is involved in the regulation of TGF-β signaling.

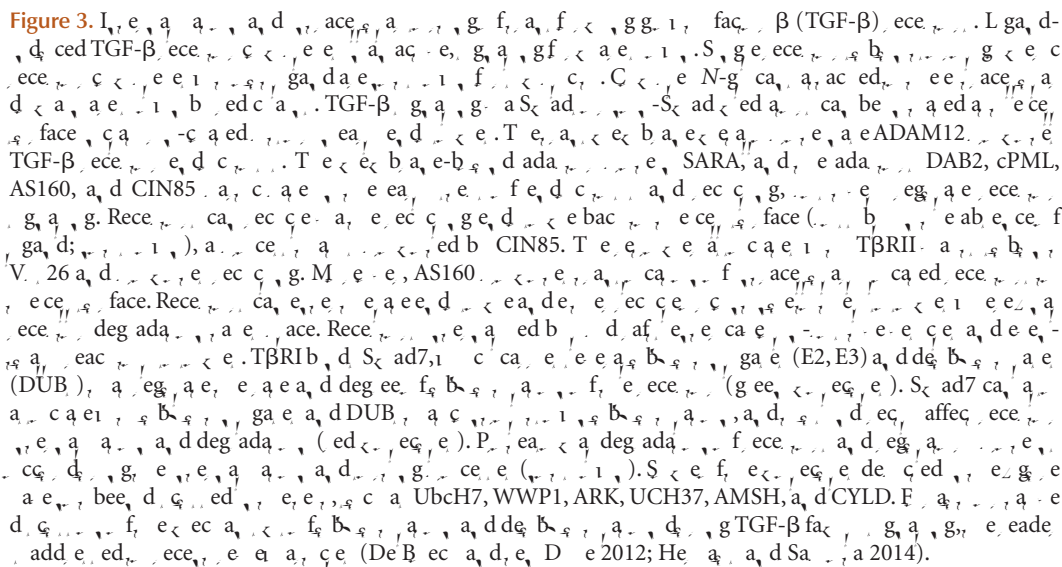
TGF-β SIGNALING IS MODULATED BY FEEDBACK MECHANISMS

The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation. The TGF-β signaling pathway is a key regulator of cell growth and differentiation.

W e ea₁ e S₁ ad. a₁ a₁ a₁ e f c₁ c₁ a₁
 a₁ ce f TGF-β₁ g₁ a₁ g₁ e e a₁ e
 a₁ -S₁ ad. g₁ a₁ g₁ a₁ a₁ a₁ a₁ ed b₁
 e a₁ a₁ ed TGF-β₁ ece₁ c₁ d₁ g₁ e

F, e e a, -S_{ad} a a, e b, ga e, ec, fac, ece -a - c a ed fac, 6 (TRAF6) a a c a, e. T e e a c, e, -b, d, g, ff, TRAF6, e a c, e b a, e. a fT β RI, a e a, ALK-6 (S, e, e a. 2008). TGF- β , e, a, ce, e b, d, g. f TRAF6, T β RI a, d e, a c a, a, ece, a e, de e, de, a, e. T e a c a ed TRAF6, e, b, a e e MAP, a e, a e, a e TGF- β a c a ed, a e 1 (TAK1), ead, g a c a, (S, e, e a. 2008; Ya a, a e a. 2008; K e a. 2009). TAK1, e, a e a, d a c a e, e MAP, a e, a e (MKK) 3, 6, 1 c a c a e, e. 38 MAP, a e; a, ee, a e f, a a b, d, S_{ad} 7, 1 c a c a a caff, d, g, e, b, g, g, e, a e c, e, eac, e a, d c, e, T β RI, e eb fac, a, g TGF- β , d, ced. 38 a c a, 38 a, a, e, e.

TAK1, α ed b TGF- β , BMP-2 a, d BMP-4 a, d, ce, ece, ed - a ed α - a, f TAK1, f ed b MKK3/6 α - a, a, d 38 MAP, a e, g, a, g, a a, a, a, α ed a e c, ca e e, d, g ea, e, b, ge, e (S b, a e a, 1998). T e, e, f TAK1 a α ed a, f BMP, g, a, g, a, ed b, e, c, g, e e, e, f, a e, c, d, c e, e e d f - fe, a, α ed (S e a, 2009), a, d ege, e ca, g, a, a defec, a, e, c, f S α ad5 (Jad c e a, 2006). I, e e, g, e, a c e, ec, c, α - a, f TAK1 e, e, ca, ed, e a, c a, fac a, a, a, c, d, g c ef, a a e, a, d, add - e defec - e. 38 MAP, a e, g, a, g



GTPa e AS160 (B. d e a. 2015). A , a c a -
ed b PI3- , a e (e.g., d i , ea c f , , e
 , a e ece ,), s c a , e , s i , ece , ;
 , s , a c a - , f s c ece , s a e ce ,
 , e , ce , b e TGF- β , s a , .

a e e ca b a f
 e ca a -de e -
 e TGF- β ece e c -
). T β RII a b d e
 e e g e 26
 de e de e a e;
 d be f c c a -
 ce e c g a d f
 e ba a e a de
 e e a ce (Y e a .
 e a a a a a -
 e S ad g a g
 ca be e a ed a d
 a e -c a ed e e e i c -
 ece deg ada (Fg. 3) (Ra a .
 a . 2001). T g a a a , TGF- β e-
 ce e a c i e S ad7/S e f2 b -
 a a c e a d a e deg aded -
 e a e a d e (D G g e e a .
 2003). N T β RII a d T β RI b a be-
 ag ca ca be e a ed b e e a -
 de e de e a - de e de e e a -
 (F ge e a . 2008). C a - de e -
 de e e a a f be ag ca e e be
 e ed f e f c e a c a f b S ad2
 a d 38 MAP a e a a . P -
 a a f be ag ca T 841 b T β RII
 e e e a c a f e caff d g -
 e - β a e i c e d a e e a c i -
 f d af a d e e d c -
 f be ag ca (C e e a . 2003). T β RII i a
 f d b d e a e b a e e a -
 e a e ADAM12 i c a e a e -
 e de e a e e e e g f T β RII
 e a e d e e e e i b d g
 S ad7 a d e e b e e e deg ada
 (A e a . 2007). C e TGF- β ece
 e a a ca a be eg a ed b e de-
 g ee f N ed g c a f e ece
 (Pa dge e a . 2004). T e β 1,6-*N*-ac e -g -
 c a a f e a e V (Mga 5) a c -
 a e eg a ed e a ca ce a dg -
 c a e e TGF- β ece ead g
 ged e de ce f e ece e e
 ce face.

B T β RI a d T β RII a e ca ed e
 ba a e a a f a ed e e a ce
 (M e a . 2004). T e de e e ba -

a e a de f T β RII de e de a
 LTA VA F e fbe e e a c d e d e
 529 a d538 e ece (M e a . 2007).
 Be ag ca a ca e e ba a e a a
 f a ed e a e e a ce a d -
 a f P 826 e e c a c d -
 a f ece ca ed f ce a
 a d d c f EMT (Me e e a . 2014).

MUTATIONS OF SERINE/THREONINE KINASE RECEPTOR GENES IN DISEASES

M a e e e c d g e e be f e
 e e/ e e a e ece fa a e
 bee b e ed a e be f d ffe e d ea e .

Malignancies

I a c a g e a e e TGFBR2 ge e a e
 c c a c a f c e e b ad-
 de ead a d ec e g a TGF- β g-
 a g e e a a a e e e e
 e e e e (Ka d e a . 2013). I -
 e e g e a TGF- β ece ge e
 a e c e c c e f e a e b ea
 ca ce a d e e a . Ca ce de e e
 e e a e e e e e f e
 be c a a e ed e a e f e e -
 f c e f TGF- β a d BMP g a g . T e
 ge e e c d g T β RII f e e a ed
 (30% f a ca e) c e e a ca ce a e
 (B i a e a . 2008). A c a a e c b a f
 c e e a a g a c i a c a e e
 ab e (MSI) a d e c ca e e
 ge e e c d g T β RII e a ed i af e -
 c f g e a 90%. MSI a e defec-
 e e c a c e a a e e a f e e -
 ead e e ca e e e e a i e e
 DNA e e ce c a g e e f ade-
 e e e d e ba ed de e e de .
 E 3 f e TGFBR2 ge e c a a ade-
 e e a c a e a d i c a bee
 ca ed a e BAT-RII e e ge e
 e e g f a e f e a e a e c de
 e e e e a ed e i d e -
 ca ed e a ece (B i a e a . 2008). I -
 e e g e de e e f c e a
 TGF- β ece a bee e e
 f e e c b a a f a e e ab e ge -

C.-H. Heldin and A. Moustakas



...ca, a, da, e, e, ce, a
...e, e, f, e, a, e, e, a
ce, a, i, e, a, ce, e, e, a, e
fe, a, e, g, a, f TGF- β (B, a, e, a, 2008).
N, T β R11 b, a, T β R1 ca, ffe, f, a
...a, e, ab, e, ade, e, a, ca, ed
b, a, c, e, a, defec, a, d, e, a, a, a-
e, e, i, a, T β R16A, a, bee, ed, e
ed, e, c, ca, ce, i, a, f, e, e, c, f
100%; i, e, e, ca, ef, e, a, a, f, c, e, f
f, c, ca, ce, a, e, ca, g, a, a, a, a,
ge, e, c, a, ge, e, a, ed, ce, a, d, b,
a, i, e, e, c, a, a, e, ca, a, e, e
e, e, e, de, e, e, f, e, a, a, a,
(B, a, e, a, 2005). A, e, e, e, f, e,
a, a, g, a, c, e, e, ed, a, a, a,
c, e, a, ca, ce, a, d, e, de, e, d, a,
a, c, e, a, defec, i, a, a, e, e
BMPRIA/ALK3 ge, e, ge, e, c, ce, g, f,
ed, g, ge, e, i, a, a, ed, f, g, a,
ca, c, f, fa, e, i, ge, e, a, g, ca,
e, e, e, e, f, ca, ce (N, e, e, e, a,
2011).

N, c, e, a, ca, ce, de, e, d, ge,
e, c, ed, a, a, a, e, TGF- β
e, e, ge, e, B, c, c, e, a, g, a, c, e,
a, d, e, ec, a, c, c, c, c, e, e, a,
f, e, e, de, e, e, a, ce, e, a, fe,
a, e, a, f TGF- β ; ca, be, a, b, ab, e
e, a, e, g, a, e, ce, f T β R1,
ca, g, a, e, d, effec, a, fa, e, e, e,
eac, e, a, a, c, e, b, a, e, e, de, g, e,
ce, b, e, B, ce, e, d, be, g, ca,
TGF- β , g, a, g (Sc, e, a, e, a, 2004).

Juvenile Polyposis Syndrome

I, e, e, d, e (JPS), a, e, de,
e, a, a, a, a, e, e, e, e,
i, c, a, ca, ed, i, a, a, ce, ed, f,
ade, ca, c, a. Ge, e, e, f, f, c,
e, a, e, ALK3 ge, e, a, bee, b, e, ed
20%–25% f JPS, a, e, (H, i, e, a, 2001,
2004). BMP, g, a, g, i, a, a, g, e,
W, a, i, a, f, c, e, e, e, a, e, ce,
c, a, e, e, ca, g, a, b, a, ced, ge, e, a,
e, e, a, e, ce, d, g, e, fe, a, f, e,
e, e, a, e, e, e, (He, e, a, 2004). I, add,
g, ca, W, - β -ca, e, g, a, g, de-

e, d, e, b, a, a, ced, a, c, f, e, PI3-
a, e/A, a, e, i, c, de, e, c,
f, e, a, a, e, PTEN. I, e, ef, e,
g, g, a, JPS, a, e, e, a, e, e, a,
ce, i, a, a, e, e, ge, e, e, c, d, g,
BMPRIA/ALK-3, S, ad4, a, d, PTEN, de, e,
g, defec, e, BMP, a, i, a, a, d, e, a, c,
W, - β -ca, e, g, a, g, e, e, e, g, a,
b, a, a, ced, e, ce, d, c, a, a, e,
e, a, c, g, i, (He, e, a, 2004). F, a,
a, a, a, f, a, e, e, e, e, g,
a, e, c, a, a, a, a, acc, a, e, e,
BMPRIA/ALK3 ge, e, a, e, eg, e, c,
g, e, e, a, c, e, a, d, a, b, e, e, ga,
d, b, d, g, e, face, f, e, e, e, (K, c, e, a,
2008). T, a, a, a, de, g, g, ge, a,
e, ALK-3 ge, e, a, a, affec, e, g, b, a, f, d,
g, f, e, e, d, c, a, f, e, e, e,
a, g, e, a, e, e, a, e, e, g,
ca, a, c, f, BMP, e, e, a, c, e,
e, e, ca, g, JPS, a, e, a, ed, ab, e.

Hereditary Hemorrhagic Telangiectasia

He, ed, a, e, a, g, c, e, a, ge, a, a (HHT)
a, a, a, a, d, a, a, a, d, de,
i, c, c, a, a, e, ed, b, a, a, a, e, a,
ge, a, e, a, d, a, e, e, a, f, a, a, I,
a, bee, i, a, e, e, g, a, a,
e, ge, e, f, e, d, g, a, d, ALK-1, ca, e,
HHT1, a, d, HHT2, e, e, e, (McA, e,
e, a, 1994; I, e, e, a, 1996; Abda, a, e, a,
2005). T, e, e, b, e, a, g, ge, a, e, d, g,
a, d, ALK-1, e, a, e, e, a, e, g, a, g, a,
i, a, e, d, e, a, ce, a, d, a, e, e, ba,
fe, e, f, e, ca, ca, e, HHT. Beca, e, ALK-
1, g, a, g, e, d, e, a, ce, i, a, f, a, d, be,
de, e, de, f, T β R11, e, ga, d, ed,
e, be, a, TGF- β , f, c, b,
BMP-9, BMP-10, a, e, e, a, a, ac,
a, a, f, ALK-1, (Pa, e, a, 2008).

Loeys–Dietz Syndrome, Marfan Syndrome, and Familial Thoracic Aortic Aneurysms and Dissections

L, e, D, e, d, e (LDS), Ma, fa,
d, e (MFS), a, d, fa, a, a, c, a, c, a,
e, a, d, d, e, e, (TAAD), a, e, d, ea, e

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- Advanced Online Article. Cite this article as *Cold Spring Harb Perspect Biol* doi: 10.1101/cshperspect.a022053

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$\tau, a_1, f, g, g_1, \tau, \text{fac}, \beta, e, \text{III}, \text{ecc}, \tau, \text{-dec}, e_1,$
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TGF- β Family Receptors

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Cold Spring Harb Perspect Biol 2016; doi: 10.1101/cshperspect.a022053

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