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.

 $T_{fa_{\zeta_{1}}}e_{\tau_{1}}a_{\tau_{1}}f_{\zeta_{1}}g_{g_{-1}\tau_{1}}f_{a_{\zeta_{-1}}}\beta(TGF-\beta)$ $fa_{\zeta_{1}}f_{c_{\tau_{-1}}}e_{ge_{\tau}}e_{ge_{\tau}}e_{ge_{\tau}}a_{33}g_{\zeta_{\tau}}a_{\tau_{\tau}}$ $e_{\zeta_{\tau}}b_{e_{\tau}}e_{\zeta_{\tau}}d_{g}TGF-\beta f_{\zeta_{\tau}}b_{e}$ $ge_{\tau}e_{\zeta_{-1}}e_{\tau_{\tau}}(BMP_{\tau}), g_{\tau_{1}}t_{\tau_{\tau}}a_{d}d$ $d ffe_{e_{\tau}}a_{\tau_{\tau}}f_{a_{\tau}}f_{a_{\tau}}(GDF_{\tau}), a_{\zeta_{-1}}e_{\tau_{\tau}}e(AMH)$ $(De_{\tau_{\tau}}c_{\tau_{0}}dA_{\tau_{0}}-M_{t_{11}}e_{\tau_{0}}2008; M_{f_{\tau}}t_{\tau}a_{\tau_{0}}a_{\tau_{0}}d$ $He^{-1}d_{\tau_{0}}2009; Ma_{\tau}ag_{\tau}e$

RECEPTORS FOR TGF- β FAMILY MEMBERS

TGF-β $fa_{\zeta_{1}} < e_{\zeta_{2}} b_{\zeta_{1}} = g_{\alpha_{1}} a_{\alpha_{1}} a_{\alpha_{2}} a_$

B, d, g, f a TGF- β fa_z, z e_z be, d ce a, e_z b, f a e e, e, a_z e, c c z, e, f₁, , ela, d_i, , ell ece , . . Te e a e e e $\mathfrak{g}_{\zeta}(a_{t,\tau}) := I_{\mathcal{I}} ece_{\mathcal{I}} := \mathfrak{a}_{t}(d_{\mathcal{I}} \circ e_{\tau}) := II_{\mathcal{I}} ece_{\mathcal{I}} :=$, $d = d_{g} a_{\zeta} e_{\zeta} be_{\zeta} = f_{\zeta} e_{\zeta} GF-\beta fa_{\zeta}$ b, d, ca, açe, cç, b, a, f, le I a, d, \therefore e II, ece (F g. 1). T e ece (F g. 2)a e, a, e, c, e, e, c, e, ace, e, a, d - ζa_1 , a_1 , a_2 , $\zeta''e_{\zeta}$ b, a_1 e d, ζa_2 , a_2 , a_{ζ} , a_{ζ} e ζ baed ca, a da aed ca; ree, e ce, f, e BMP, e II ece, a, d, c, $a_{i} a_{i} e_{i} e_{i$ b, e, a, f, e, a, e, a, a, e, e, Lga, d-, d, ced, g < e, a, , f, eI a, d, e II, ece f_{1} , f_{2} , e_{1} , e II, ece f_{2} , e_{2} , e_{3} , e II, ece f_{2} , e_{3} , e II, e \ldots a_{-} , f_{t} , e_{t} , e_{t} , e_{t} , e_{t} , a_{t} g_{1} , f_{1} , e_{g} , a_{ζ} , e_{ζ} , b_{z} , e_{d} , c_{ζ} , a_{z} , c_{ζ} , c



Figure 1. So $e_{\zeta} a_{\zeta} c_{\eta} f_{\tau,\eta} a_{\tau,\tau} = f_{\tau} e_{\tau} e_{\xi} e_{\zeta} e_{\delta} b_{\eta} f_{\zeta} e_{\zeta} b_{\theta,\tau} f_{\tau} e_{\tau,\eta} a_{\tau,\tau} f_{\tau,\zeta} g_{g-1,\tau} f_{q} f_{q} \beta_{\tau,\tau} \beta_{\tau,\tau} f_{\tau} e_{\tau,\eta} a_{\tau,\tau} f_{\tau,\tau} e_{\tau,\eta} f_{\tau,\tau} f_{\tau,\tau} g_{g-1,\tau} f_{\tau} f_{q} f_{\tau,\tau} \beta_{\tau,\tau} f_{\tau,\tau} e_{\tau,\eta} f_{\tau,\tau} f_{\tau,\tau} g_{g-1,\tau} f_{\tau,\tau} f_{\tau,\tau} g_{g-1,\tau} f_{\tau,\tau} f_{\tau,\tau} g_{g-1,\tau} g_{g-1,\tau}$

, g c, e a, d e, e e d e (GS d z a,), ca, g aç a, f, a e.

T $e a c \rightarrow a e d_t \rightarrow e I_t e_t + e_$ ece , , , , , , , , , , , , , a e z ez be, f e ece $-a_{\zeta} - a_{\zeta} - a_{\zeta} + a_{\zeta}$ TGF- β , aç , a d , da ge e a , d. ce a_1 , $f S_z$ ad $2a_z$, $d 3a_z$, e_z ea BMP, ge, e, a, a_1 , a_2 , a_3 , a_4 , b_5 , a_4 , d_8 (Fe, g a, d De, c 2005). Ac a ed R-S_c ad t e, f, z t, z e, c c z , e e, t t e c z z , ζ ed a_{1} , S_{ζ} ad4, 1 c 'a e_{1} , a_{1} , c_{z} ed a_{z} , e"ęçę, 1 e, e ç. e, a e i , ., e, a, $c_{1}, c_{2}, c_{1}, c_{2}, c_{2}, c_{2}, c_{2}, a_{1}, d_{1}, c_{2}, e_{2}, e_{2}, c_{2}, c_{2},$ $eg_{e_1}ae_{e_2}e_{e_3}e_{e_4}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_5}e_{e_$ Teeaea, , -S_c ad, g, a, g, a, 1 a, ac_{γ} , a_{γ} , c_{γ} , d_{γ} , c_{γ} , c_{γ} , d_{γ} , g_{γ} , c_{γ} , d_{γ} , g_{γ} , g_{γ} , d_{γ} , , eE 1/2, JNK, a, d. 38 MAP , a e. a 1 a , (PI3)- , a e, a, d R GTPa e (M_{f}) , a a a, d He d , 2005).

T e., e e, $c \leq \zeta_{\mathfrak{s}}$, ca., $f \in e_{\mathfrak{s}}$, e $f_{\mathfrak{s}} \in \mathcal{S}_{\mathfrak{s}}$, a a d f $\zeta_{\mathfrak{s}}$, a c a ac e, $c \in f_{\mathfrak{s}}$ e $f_{\mathfrak{s}} \in I$ a d $f_{\mathfrak{s}} \in \mathcal{S}_{\mathfrak{s}}$, a c a ac e, $c \in f_{\mathfrak{s}}$ e $f_{\mathfrak{s}} = I$ a d $f_{\mathfrak{s}} = II$, $g_{\mathfrak{s}}$ a g TGF- β ece $f_{\mathfrak{s}}$. (F g. 2); $1 \in \mathfrak{e}$, $1 \in \mathfrak{e}$ a $f_{\mathfrak{s}}$, $g \in \mathfrak{s}$, \mathfrak{e} $f_{\mathfrak{s}} = \mathfrak{e}$, \mathfrak{s} , \mathfrak{e} \mathfrak{s} ece $f_{\mathfrak{s}}$. $f_{\mathfrak{s}} = \mathfrak{e}$, \mathfrak{s}

TGF-β SIGNALS VIA A HETEROTETRAMERIC TβRI•TβRII COMPLEX

T e_{τ} , ee TGF- β , $f_{\tau} \leq 1$, TGF- $\beta 1$, TGF- $\beta 2$, a d TGF- $\beta 3$, b d , a , g e_{τ} . e II , ece , (T β RII). H 1 e e, add, $e_{\tau} = e_{\tau} e_{\tau} b_{\tau} =$ $e_{\tau} e_{\tau} e_{\tau} e_{\tau} e_{\tau} = I$, ece , (T β RI, a, ca ed ac , ecc , - e , a e 5. ALK-5), $e_{\tau} e_{\tau} e_{\tau} e_{\tau} = e_{\tau} e_$

Bef e ga db d g, $T\beta RI a d T\beta RII$ c c_{i} , $a_{i} < c_{i}$, $c_{i} < c_{i}$, $d_{i} < e_{i}$, $a_{i} d = e_{i}$, $d_{i} < e_{i}$, $a_{i} < e_{i} < e_{i}$, $d_{i} < e_{i}$, $d_{i} < e_{i}$, $d_{i} < e_{i}$, $d_{i} < e_{i} < e_{i}$, $d_{i} < e_{i} < e_{i}$, $d_{i} < d_{i} < d_{i}$, $d_{i} < d_{i} < d_{i}$, $d_{i} < d_{i} < d_{i}$, $d_{i} < d_{i}$, $d_{i} < d_{i} < d_{i}$, $d_{i} < d_{i}$,

T e , , , a TGF- β b, d, g, d, ce a $e_{e_{\tau}}, e_{a_{\zeta}} e_{c_{\zeta}}, e_{\tau} f_{\tau} I_{\tau}$ TBRI a, d , $\Gamma T\beta RII_{\zeta_{\tau}} e_{\zeta_{\tau}} e_{\zeta_{\tau}} e_{1} a_{1} a_{1} a_{1} e_{1} e_{1} e_{1} e_{1}$ b de s g d ffe e, a ece , agg g (M_s, a a e a 1993; He, e a 1994; We e a. 1999), 1. -d c e, ..., a ge e e c, ... e (Ya₅ a , a e a . 1994), a d ge e c c ₅ . eς e, a, , (We, -Ga c a a, d Ma, ag e 1996). Me ecent, , the cap a te de ae 1, , a_{τ} , ed_{τ} 'e $cTGF-\beta_{\tau}$, ec_{τ} , eb_{τ} , d_{τ} , 1_{τ} $T\beta RIa$, d_{11} , $T\beta RII_{\zeta_{12}}$, $e_{\zeta_{12}}$, $e_{\zeta_{12}}$, g_{12} ζ e, c 2:2:2 ζ ζ , e. T e TGF- β ζ , e. ζ e ezbeit a d- e e ce e, a a e a e_z bed a a, i a a, e z a, e a da e e d , ge e b a d e, de b d , e, 1, , jeg, $.TGF-\beta c$, ac, $T\beta RI_1$, $e_{,2}$, $ge_{,1}$, a, d T β RII 1, , e, e, de, de, f, e, ge, (Ha, e a. 2002; G. . e e a. 2008; Radae e, a. 2010). I, add, , , d ec ece , , ece - $\mathbf{e}_{\mathbf{r}}$, $\mathbf{e}_{\mathbf{r}}$ e, $\mathbf{a}_{\mathbf{r}}$, $\mathbf{c}_{\mathbf{r}}$, $\mathbf{b}_{\mathbf{r}}$, $\mathbf{e}_{\mathbf{r}}$, $\mathbf{e}_{\mathbf{r}}$, $\mathbf{a}_{\mathbf{r}}$ ced, $\mathbf{ab}_{\mathbf{r}}$, f, e, ece, , ga, d ç , e (Radae e a. 2010).

TGF- β 1 a, dTGF- β 3 b, dT β RII1, g e af, , , a, T β RI. T , , , e b, d, g, c, , β , T β RII; , e eaf e, T β RI , e , ed β , e c , e b , ec g, g a, β e , e face ge, e a ed b , e TGF- β T β RII c , e (G, e e a, 2008). I, c , a, TGF- β 2 , 1 , a e , 1 af, β T β RII; β , e e , c ece , β c a be ag ca, a , f GF- β 2 , e e (e e f, g) ab e ece , c , e e (e e f, e b, g) ab e ece , c , e e (e e f, e b, f).

T e $f_{\zeta \zeta}$ e, f, e c ζ_{\cdot} , e bei ee TGF-β a d f_{\cdot} ece, f_{\cdot} e c ζ_{\cdot} , e gge f_{\cdot} a f_{\cdot} e f_{\cdot} a f_{\cdot} fTβRI•TβRII ζ a g a a de e de f_{\cdot} a f_{\cdot} fTβRI•TβRII ζ a g a a de e de f_{\cdot} a f_{\cdot} fTβRI•TβRII ζ a g a a de e de f_{\cdot} a f_{\cdot} fTβRI•TβRII ζ a g a a de e de f_{\cdot} e $f_{$

BMP ece \dots b d e (ga d , ga d , ga



Figure 2. Sc e_{ζ} a c_{1} , f_{1} , g_{2} , f_{1} , e_{ζ} a q_{ε} , q_{1} , f_{1} , g_{1} , g_{1

, eBMP, ece, b, d, , e, ece, , $\zeta \zeta$, e , e a, e, , e, af, a, e, c, e , d, g af, e, fTGF- β 1 a, d, ece, (Seba d e a. 2004). T, ead, ag ea e e b, b 1 c BMP, ca, g a, g a, g a, e d e, e, e, f ce, face, ece, (Fg. 1). A , e ca e f, T β RII, e, e, a, e c BMP , ece, c, e e a e, ab, ed b, e ac-, be1 ee, e e c, a, c c d c a, f, e , ece, (N) e e a. 2002). S c c, a, c c

ce $f_{1,2}$ T e $f_{1,2}$ e $f_{2,3}$ e

TGF-β RECEPTORS ARE REGULATED BY PHOSPHORYLATION

Teac, e, fb, TβRIa, d TβRIIa, e eg, a ed b e e a, a., e e, (e'e ed b W g', e a. 2009a). Af e ga, d-, d, ced a, e_{ζ} b, f_{τ} e, e_{τ} , e_{τ} , a_{ζ} e, c TGF- β , ece, β , ζ , e , e , e , e , e , eaç e TβRII , e GS d a,, ca ed en el eac f, e, a e d _c a _e (Fg. 2) (W a a e a . 1994). T e _ _ e d e (.e., T 186, Se 187, Se 189, a d Se 191); , a . ea, , a , , , ge e d e , f $c_{g} c_{q} c_{q} c_{r}, a_{r} ce f$, $a_{r} c_{q} a_{r}, b_{r}, e e$ eed be a ce, a, ab e a ce, a, , e, d, , a ea'f, aq a, f, e TβRI , a e. T e , , a , , ead , a c,f, ca, a, ca, ge, a, ca, e, e, e, e, e, e, f , e12 Da- ((, FK506-b , d , g ... -, e, (FKBPI2), 1 c b, d, e GS d z a, a, d, b, , $eT\beta RI$, a, e(Wa, ge, a, 1996;Се, е а. 1997; Ц е е а. 1999). Те. _ -..., a., f, e GS d (a, f), e, e, e, e_1 a, ce_1 , e_2 a, e_1 , $R-S_{\zeta}$ ad h_1 c_2 -(H, ee a. 2001). T e , a e aç , f T β RII , eg , a ed a, a Se 416 (F g. 2) (L, a d L d, 1997). e, e, e, e, e, e, e, e, c, d, g T, 259, T, 336, a, dT, 424, 1 c a, z a ç, b, e, e, e $eg_{1}a_{1}$, $f_{1}e_{1}a_{2}e_{3}a_{4}$, $fT\beta RII (La$ e e a. 1997), a db Sca T 284 (Ga e a, d Sc e_{ζ} a, 2006, 2007); T 470 (a_{1}, a_{2}) , a, e, e, b S, c, a, ..., -, a ed (C e, e, a. 2014). T e_{2} , d, g, a TβRII, e. e. a ed. e. e. e $c_1, a_1, g_2, g_3, g_{\zeta_1}, e_{\zeta_2}, e_{\zeta_1}, e_{\zeta_2}, e_{\zeta_1}, f_{\alpha_1}, \dots, e_{\zeta_n}$

 $f_{1} = f_{1} = 284$ a bee, $f_{1} = 1$, $f_{2} = 1$ $g_{1} = b$, $d_{1} = g_{1} = f_{1} = ada_{1}$, S = c, d = d, $g_{2} = f_{1}$, $g_{2} = 1$, S = 1, $a_{1} = g_{2} = g_{1}$, $d_{2} = a_{2} = a_{1} = 1$, $f_{2} = a_{1} = a_{2} = a_{1} = 1$, $f_{2} = a_{1} = a_{2} = a_{2} = a_{2} = 1$, $f_{2} = a_{1} = a_{2} = a_{2} = a_{2} = 1$, $f_{2} = a_{2} = a_{$

TβRI ca, be a ed a Se 165 , $e_{\mathfrak{s}}$, $a_{\xi} e_{\xi}$ b a ed ξ a $(S_{\mathfrak{s}} c e_{\xi})$, e a 1996). L, e e, g , $\zeta = d_{\xi} a_{\xi} e_{\xi}$ TGF-β g a g; g 1, $\mathfrak{s} = e_{\xi}$ a d $\xi a_{\xi} = d_{\xi} \zeta_{\xi}$, a e e a ced af e $\zeta_{\mathfrak{s}}, \mathfrak{a}_{\xi} = f$ Se 165, 1 e ea , e = a $\mathfrak{s} = \mathfrak{s} + \mathfrak{s} + \mathfrak{s} = \mathfrak{s}$ effeq dec ea ed.

 S_{ζ} , a_{1} , $T\beta RII$, e_{1} , e_{2} , a_{1} , e_{2} , a_{2} , a_{3} , e_{2} , a_{3} , e_{2} , a_{3} , e_{2} , a_{3} , b_{1} , e_{2} , e_{1} , e_{2} , e_{2} , a_{3} , e_{2} , a_{3} , e_{2} , a_{3} , e_{4} , e_{2} , a_{3} , e_{2} , a_{3} , a_{4} , e_{2} , a_{3} , e_{2} ,

T e a_{1} , $f'TGF-\beta$ ece a_{1} , $be c_{s}$, e a c e d b e e a, a, a, e, . T , , GADD34, a, eg, a, . $f_{s} b_{s}$, $f_{t} e_{t}$, e_{t} , $a_{t} e_{t}$, $a_{t} e_{t}$, $b_{t} d_{t}$, $b_{t} d_{t$ b, d, $T\beta RI$; ePP1 ca a, cac, , e eb $ec_{\mathfrak{s}}$, $ed_{\mathfrak{r}}$, $T\beta RIa$, $dde_{\mathfrak{r}}$, $a_{\mathfrak{r}}$, eece, (S e a. 2004). I e d, e a ce, , PP1α₁ a 1, de , a e ALK-1, $b_{r, r, r}$, e_{s} , $b_{s, r, s}$, TBRI, ALK-5 (Va d ζ a, d, ,, e, a. 2006). Τ e PP2A. , , a, a, e , $a_{\mu} = \zeta_{\mu}$, ca, ca, cd, $TGF-\beta$, ece_{μ} , de_{μ} , -, a., I, e, e, g, e, e, e, e e a ed PP2A f_{α} b, f_{α} B α a, d B δ f_{α} d, a e TGF- β , g, a , g ,..., e1 a ; 1 e ea, e Bα s b, , e, a, ce, TGF- β , g, a, g, ζ_{-n} , e, b, ab, -, g T β RI, e B δ_{1} , b_{1} , c_{2} , c_{3} , c_{4} , c_{5} , c_{6} , c_{7} , TGF- β_{1} , g-, a, g, ζ, i, e b, b, g, eTβRI, a e aç (G 1. d-P e, e e a 1998; Pe, c e, a. 2000; Ba_s, e, a. 2008).

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

TGF- β , $\zeta_{\mathcal{F}}$, $a_{\mathcal{F}}$, $a_{\mathcal{F}$

ga e c-Cb (Z_{e} , e a. 2013). c-Cb , 1 a $a_{g} b_{g}$, E3 ga e a d a ega e ζ_{e} d a f_{ζ} a , E_{g} , e a e ece, b_{i} , a bee, 1, b_{i} be ca ab e a f. edd a g bee, 1, b_{i} be ca ab e a f. edd a g e e de ζ_{g} a g_{1} , fac, (EGF) ece, (O ed e a. 2006). Nedd a f T β RII a L 556 a dL 5671 a f_{g} , d_{i} f β e e d c f_{i} e ece, f_{i} e ece f_{i} e e d c ξ_{i} a f_{i} e ece f_{i} e e d c ξ_{i} a f_{i} e ece f_{i} e e f_{i} e f_{i}

Q₁, l₁ edge ab₁, ₁ b₁, -ba ed ζ ec a, ζ , ζ a, eg, a e BMP, ece, f, c e_{χ} , e_{χ} a , a a_{χ} , e_{χ} , e_{χ} , e_{χ} age c_{χ} , a ed 1, $TGF-\beta$, ece, β , M_{at} , M_{at} , de, $a \in c$, ce, a, ed., e BMPRII, 1 c a de c bed ab e, af e de , , , , f BMPRIA/ ALK-3 b, e_{μ} , e_{μ} , a_{μ} a_{μ} a_{μ} b_{μ} , a_{μ} d_{μ} beç ç e ..., s b s , a ed a d deg aded (Sa 1 e a. 2006). U de . a ... g ca ç d ..., sc'a Ka, açzaa d'ce, a', z. za ca, ed b, feç, 1, e Ka, a ç z a a caed e, a a e c ded b e , , -ga e , f b e , a e BMPRII a d e ", z a deg ada, (D, g, e a. 2010). U, de c. e. , g ca c, d,., , e $E3_{\mathfrak{s}}$ b, $\mathfrak{s}_{\mathfrak{s}}$, ga e \mathfrak{l} c \mathfrak{c} ed a e BMPRII ., sks, a, a, ea, , s, c, a e, d e a ce, (D, , g, , e a 2010). F, a, , e DUBUSP15, a de b, , a e a d, ab, e T β RI, a, de b, , , a e , e BMP, e I ece , BMPRIA/ALK-3, ca, g, ab, a-, a de, a cez e, fBMP, g a g a, d, (He, a, e, a, 2014). W e ea USP15, a ge, T β RI b b, d, g, S_z ad7, USP15 ac, BMPRIA a S_{ζ} ad6, e e, g ac, e, ed c ec a, c, f ece, de b, e, $a_{-}, a_{-}, e_{-}, b_{-}, (I)-S_{\zeta}$ ad (Ec_{-}, c_{-}) e a. 2012; He a, e a. 2014).

CONTROL OF TGF-β RECEPTOR EXPRESSION BY microRNAs

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

e e e_{t} , ece e_{t} , ζ RNA , e fa ζ , a bee. e_{1} , e_{1} , e_{2} , e_{3} , e_{5} , e Reg_{a} , f, ece_{a} , e, e, e, b, RNA, bca, $a \in ace d_{g}$, g_{g} , z_{a} de e_{g} , $z_{e_{1}}$, s, de la graca, c, d, , s, c a e -, e, ..., , ca, ce, ..., a , feq., . T e faq , a a g e, ece , ζ RNA , e TGF- β faz ca, be eg, a ed b < a, < RNA, a, d, a à gie, c RNA, a ge, e e a , e c RNA , add, , , , e g e, , ece, , , ge, e a e, a ς_{ζ} , e_{j} , e_{j} , f_{ζ} , $RNA-\zeta$, ed_{i} , ed_{i} , ed_{i} , a_{i} , , c, i, a c, ..., Heeled, c, eeced $e_{a_{\zeta}}, e_{f_{\varepsilon}}, f_{\varepsilon}, c_{\zeta}$ RNA, $a_{\varepsilon}, de_{g_{\varepsilon}}, d$ $e_{a_{\zeta}}$, e_{z} , f_{z} , e_{ζ} , e_{z} , I_{z} , $e^{TGF-\beta}$, a_{z} -1 a, T β RII ζ RNA , a ge ed b , e e a ζ RNA , c_{fs} d , g ζ R-302 a, d ζ R-372, $1 c d 1, -eg, a e, e e, e, f T\beta RII$ de, g, e, e, c, f, de ced, e, e, e_{ζ} - e_{ξ} ge, e, a, $(S_{\xi} b) a_{\zeta} a$, a_{ζ} e, a, a, a_{ζ} e, a, b, 2011). T β RII d 1, - eg, a, e, a, ce, e déd ffe e, a, , , ce, a, d, , , e, a, e, e, c ¿ a re e e a ra re r a je r ed $\mathbf{f}_{i,t} = \mathbf{e}_{i,t} \mathbf{a} \mathbf{b}_{i,t} \mathbf{c}_{i,t} \mathbf{e}_{i,t} \mathbf{f}_{t} = \mathbf{e}_{i,t} \mathbf{e}_{i,t} \mathbf{c}_{i,t} \mathbf{e}_{i,t} \mathbf{c}_{i,t} \mathbf{c}_{i,t} \mathbf{c}_{i,t} \mathbf{c}_{i,t} \mathbf{c}_{i,t}$ a d ffe e, c, e, , R-302, 1 c, d, ced b c, $e_{t} - e_{t} - e_{t}$ ca, ed CCN2), a ge, $T\beta RII_{\zeta}$ RNA a, d, e eb b_{1} , $d_{1}e_{2}b_{2}$, (Fa $e_{1}e_{2}a_{1}$.2012). O₁ e, e a, d, d, g, ge, f d, e $2 b_{r}$, TGF- β , g, a, g, a, c, a_{r} , e e_e , e_ζ , $R_{\gamma}e_{\gamma}-7b$ (c_{ζ} , γ , 1, a_{γ} e_{1} , e_{2} , e_{2} , e_{2} , e_{2} , e_{2} , e_{2} , e_{3} , e_{4} , e $T\beta RI$ RNA e e_{1} , a, d, e_{1} , R-e -7b , e, e, , b TGF-β ca, e TβRI, d, c, a, de, a, ced, g, a, g, d, e, $1 e e_2 b_2$ de e. . (Ya, ge a. 2013; Wa, ge a. 2014). I, s_{ζ} a, ca, ce, e_{β} , e_{β} , f_{β} T β RII ca, a, bed 1, - eg, a ed b (RNA, f c a a, d R-373, b, ea, ca, ce, (Me, dag e a). 2010; Ke, g, e a. 2012). C, ca, e a-, ce, s, a ca c, z a ge, , , e d 1, eg_{a} , $fT\beta RI/ALK-5e_{a}$, b_{ζ} R-140-5. (Ya, g e, a. 2013; Wa, g e, a. 2014).

Ea, f, g de e, ζe_1 , \ldots ec 2 ed b, da g, a, g, a, d, e, a, a, e, $\zeta = 1$, f, e e $\zeta = 1$ b, $\zeta = ce_1$, a, e, d_1 , d_2 , d_3 , eg, a ed b, $1 - \zeta = c$ be, f, e < R-15 fa ζ , $\zeta = R-15$ a, d $\zeta = R-16$, 1, c, a ge, e A $\zeta = R$ II, ece, ζ

^c RNA (Ma, e, e, a. 2007). T e e e, e, . f_1 e, a_{ζ} e, f_2 e II, ece f_2 , ca, be d_1 , - eg -, a ed b < R-181a, g a, s, a centre f, e - a-, 1 c d ffe e, a e , e, e, e, aç , (Z a, g e, a, 2013b); aq , , , g, a, , g, e, e, e, e κ R-181a é , e , κ , κ , a , τ , e II, ece, κ , ca, be e g_{1} , ed a_{1} , $g_{1} \ge ca_{1}$, $g_{1} \ge ca_{1}$, $a_{1} \ge f_t = f_t = f_t$, $f_t = e_t e_t$, $f_t = H_t e_t$, $f_t = H_t$, $f_$ Aç RIIB, ç, e e RNA, e $\varphi_{11} e_{12} f_{12} = \zeta q^{\prime\prime} d_1 e_{12} \zeta \varphi_{11} q_{13}$, $\beta_1 = \varphi e_{13}$ d, e, e, a, a', _, gc, d, e, , c a, aç e, ed b d 1, - eg, a ... f (R-141, (R-192, ζ R-194, ζ R-200c, a, d ζ R-215, a, d ζ , e-', e, e, -, eg, a, , fAc, RIIB, , e de e, g, e b, a, z a (Se, a, a a e e a. 2012). T e e e_1 , f aç d_1 , da , e I e e -Aç RIB/ALK-4 a, d Aç RIC/ALK-7 , a, , ega e ega edb RNA; , , , a a_{1} a g_{2} a ce_{11} , ALK-4 c_{12} RNA c_{12} a ge_{12} ed b < R-145,1 c ¢ , , , ce, , fe a . , (Ya, e, a. 2012). D_e, g e, , e, , e ALK-4 CRNA, a ge ed b CR-24; ALK-4 dı, - eg, a., je, ed, a ea, age fe, de, dffee, a, ca, ge, (Wa, g e, a, 2008). D_e, g b, ea, ca, ce, aa, d'a, g, ge, e, , , e ALK-4 , RNA d1, - eg, a ed b < R-98; beca, e ALK-4 . . . e ć , b, e, b ea, ca, ce < e a, a- $, , , \zeta = R-98 a \zeta, a, a \zeta, e, a, a \zeta, e, a, a, f, e, f, f, (S) a$ ga_{ζ} e a 2012). F, a, , , , a, a, ca, ce, , e , da/ALK-7, e, , e, , a 1 a , , aç a ed b ζ R-376c, 1 c d 1, - eg, a e , e ALK-7 ece, , , , , , , , , g , a < R-376c a a ge c effec (Ye e a. 2011).

, a , s , , e e, e, f BMPRII, g, a, g , de e , g e , (S, e a 2013). A, e re, de e, d, a ç, a krizer ce, çe ce₁₁ fe a , , 1 c , b, ed b BMP g_a , g_a , g_a , $d_{-\kappa}$, ed b TGF- β ; TGF- β c_{a_1}, e_{ζ} R-17_s, -, e_{a_1}, d_{ζ} , g_{ζ}, e_{ζ} , g_{ζ} , g_{ζ}, e_{ζ} , g_{ζ} , g_{ζ 1 c d 1, - eg, a e BMPRII e e, a, d ¢, (L. e a. 2014). D. g. e de e . $z e_1 - f_{e_1} z = a_1 e_2 a_1 = a_1 e_2 e_1 e_1 = a_1 e_2 e_1 = a_1$ (PAH), $e_{1}e_{2}$, -6, $g_{1}a_{2}$, g_{2} , a STAT3 e_{2} , -6eg, a, e, e_{ζ} R-17 c_{β} , e_{z} a, d c_{a} , e_{z} BMPRII di, - eg, a., a a, ca f, ...a - gca, c, d, , (B, c, e, a, 2009). A, e, a, e, , BMPRII e e ca a be d 1, - eg a ed $b \in R-21 d_{g}$, g PAH (Pa e a 2012).

RNA a e a f f e f TGF-β g, a, g, ζ a g, a, ce. I, g, ζ a, BMPRII d 1, - eg, a , ac e ed a R-(W_g e a. 2012). I_g , e $a_{\zeta} e_{\gamma \in \zeta_{+}}$, e, ^c R-656[°], a ge BMPRIA/ALK-3[°] RNA; $1 e e, e = e_1 + f_{\zeta} R-656 f'e_{\varphi} e_{\eta}$ dı, - eg, a ed, f a, g a (G, e a. 2014), 1 c a ad ca ba ed , e e, ab-, ed, s c, -s ..., e, e, f BMP, g, a, g e, e, e, a, d, BMPRIB/ ALK-6 e e_1 , d_1 , e_g , a, d_r , R-125b , b ea, ca, ce, ce, $(Sae_{1} < e, a)$. 2009). B ea, ca, ce, a e_1 , 1 a e_2 e. f c., <., < , e 3'z, a, a ed, eg, f BMPRIB/ALK-6 CRNA 1 e e CR-125b b, d, , d, , , , , g, e d 1, -, eg, a, , , , c ec a-, z a d c a aç e g a e, i , g e f, d, ea, e, g, e, , (Sae, K, e, a, 2009). T e a_z e ..., z a bee, c ,- $\Delta_{1,\zeta}$ ed $(1, z_{1,\tau}, a, e)$ ca, ce, (1, c) ge, e, a, e, a ca, ce, ce, b, , a, e, e (Fe, g, e, a, 2012), 1 e ea e d c e c e c e c e c e $\sim_{\mathfrak{s}} e_{\mathfrak{c}} ce_{\mathfrak{c}} f_{\mathfrak{c}} e_{\mathfrak{c}} R-125b_{\mathfrak{c}}, e_{\mathfrak{c}} f_{\mathfrak{c}} e_{\mathfrak{c}} R-125b_{\mathfrak{c}}$ f, e e e a ed BMPRIB/ALK-6 ece , g-, a , g (C a, g e a . 2013).

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

 ζ R-365, a ge, e $3'_{3,1}$, a, a ed eg, f ALK-2 ζ RNA (M, a e a 2012); d 1, eg, a, fALK-2 ζ RNA b ζ R-148a, e e a, f, e ca ce, e ζ - ce, a, a, e a, ce, a ca c, c a (L e a 2015); e e, BMP, g, a, g, c, d, a ed 1, e ζ e, a, f, ; a, d, af e de e, f e e, ζ R-130ae, e, f, e e, f g, a, g, ead, g, d 1, eg, a, f, e BMP, a ge, ge, e e c d, 1 c, d ce e e, e, e, e, a, eg, a e ζ e, a e, c, c a e, a eg, a e ζ e, e, a eg, a e, c e, a e ζ e, a e, c e, a eg, a e, c e, a e ζ e, a e, c e, a eg, a e, c e, a e ζ e, a e, c e, a eg, a e, c e, a e ζ e, e, e, e, e, e, e, a eg, a e, c e, a e ζ e, a e, c e, a eg, a e, c e, a e ζ e, a e, c e, a eg, a e, c e, a e ζ e, e, e, e, e, e, e, e, e, a eg, a e, c e, a e ζ e, a e, a eg, a e, c e, a e ζ e, a e, a eg, a e, c e, a e ζ e, a e, a eg, a e, c e, a e ζ e, a e, a eg, a e, c e, a e ζ e, a e, a eg, a e, c e, a e ζ e, a e, a eg, a e, c e, a e ζ e, a e e, a e ζ e, a e ζ e, a e e, a e ζ e, a e e, a e ζ e, a e

SIGNALING VIA TGF-β RECEPTORS IS REGULATED BY CORECEPTORS

Betaglycan/TβRIII

Be ag ca (a, ca, ed, e III TGF- β , ece,) a , a, $\zeta \in \zeta$ b a e , e g ca 1, b, c, d, e , e , a e a, d e a a, e , a e acc a de c a, (L e - Ca, a e a. 1991, 1993). T e e, ace, a d ζ a, f be ag ca, a, 1, b, a , b bd ζ a, e a a ed b a, e d ζ a, e e , ga, d b, d, g a, d e a a e , c, b, e , ga, d b, d, g a, d e g e f ζ , a g -af, ga, d-b, d, g , e (Me, d a e a. 2009). T e , acc a de

c a, $a \in [a, c]$, ece, $a \in f$, TGF- β b, d, g; $c_1, a_1, a_2, ge_{1}, acc a de c a_{1}, c a e$ ε b TβRI TβRII, e ac, a d, ε, b, TGF- β , g, a, g (E c e be g e a. 2002). Be ag ca, a bee, $1, \frac{1}{2}, \frac{1$ a, d, , -S₅ ad , g, a, g (Y, e, a, 2007). H₁ e e, be ag ca, b, d TβRI a, d TβRII, de e de, , a d e e e e f e f be ag ca MDA-MB-231 ce 1 a f_s , d , b, TGF- β -, d, ced S_z ad2 a, d S_z ad3. , a., (Ta a e a. 2015). Be ag ca, ba, a e a ca ed , a ed b ea, e, e a ce, a d f_{1} f e ba a e a ca a f_{1} e ca a f_{2} e EMT (Me e e a 2014). T g_{1} , de e d g_{2} e, e, , e, a, d, e, bce, e, a, ca, a, , be ag ca, ca, $1 \neq \zeta_{-}$, e_{-} , e_{-} , e_{+} , e_{+} , TGF- β_{-} , g-, a, g.

Tee, ace_{re}, a, d, _c, a, fbe, ag, ca, ca, be e ea ed b , e, , c ç ea age; beca, e, e _r bee, ace_{rs} a d ζ a, e a, TGF-β b, d, g ca. ac, , , ac, a, a, caff, d, a, , b_{τ} , TGF- β , g_{τ} , g_{τ} , g_{τ} (L. e_{τ} -Caⁱ, a_{τ} , e_{τ} , a_{τ} . 1994). T ce b g ca e a, a be ag ca $\zeta_{\mathcal{F}}$, a b edd g e, a ce ce $\beta_{\mathcal{F}}$, a c ce $\beta_{\mathcal{F}}$, b TGF- $\beta_{\mathcal{F}}$, e - \dots , e e . e ζ e, 1, be ag ca, $\zeta_{\mathfrak{F}_{1}}$ a, η , a, 1, c, e ef c e, ..., e, , c, edd, g e_f, ed, e_fa e ed c, f ce_r, a e e_{1} , e_{2} , $TGF-\beta$ (E de b ϵ_{2} , e_{1} , 2014). Mee, be ag ca e, e, 1 a f, d, dec ea e de , g b ea, ca ce , g e , a d 1 be ag ca, e e, c, e a ed, ..., g-, ; be ag ca, a ea, $b_{1,2}$, $b_{1,2}$, a, b, deg, geç d, a, edd, g , e eb je e, e, g a, d , b, , g TGF-β (D, g e, a. 2007).

Be ag ca, ξ a a e f, ζ_{+} , a g bed. e e, g, e, ga d, T β RI a d T β RII. K, $c_{-\beta,\tau}$ f, e be ag ca, ge e $e_{\beta,\tau}$, e_z b, c, e, a, (S, e, e, a, 2003); be ag ca, a bee, 1, e, e, e, a, 2003); be af, d, g, e, e, a, e, a, d, e eb ac, a e Cdc42 a, d, b, ce ξ g a, (M, e e a, d B, be 2009) a, d, e ec, ξ g a, (M, e e a, d B, be 2009) a, d, e ec, ξ g a, (M, e, e) f, e, a, b, e, ac, g 1, b, b, a, g, 1, fac, 2 (FGF-2) a, d FGF, ece, 1 (K, e, e, a, 2013). Be ag ca, a a, bee 1, 2, 3, 4 (FGRI a, d T β RII, af c, ga, d g, a, g (e e f, e, b, 1).

Endoglin

 $E, d, g, c_{g}, a, 1, \dots, ce, f, \zeta, e$ a_{ζ} c, a_{γ} , f 47 a_{ζ} , a_{ζ} d, e_{ζ} d, e_{γ} , d_{z} (S)-e, dg, 1, ac, ac c, a, f 14 a_{ζ} , acd e_{ζ} d_{ε} e_{ζ} (Ve a_{ζ} e_{ζ} a_{ζ} . 2008). I, e e, g, L-e, d g, e, a ce g-, a , g · a ALK-1, aç · a e Id1 e . e . , 1 e ea S-e, d g, , , , , e, g, a, g a ALK-5, de cel a c ge, ac a b $r \rightarrow -1$ (PAI-1) e $r \rightarrow e_{r}$. T e c $r \rightarrow a_{r}$ c, a fL-e,dg, ç, a, aPDZ-b,d,g <-, f, 1, 1 c', , e aç, 1, GAIP, , e aç, g e_{τ} , e_{τ} , c_{a} , b_{τ} , e_{ζ} , e_{ζ} , (GIPC), a_{τ} caff, d-, g., e, , i, , , eg, a e ce, -s, face, ece, e, e, a, d, af c, g (Lee e, a, 2008). T g, e TGF- β -, de e, de, g, e $a_{\zeta_1}, c_{\zeta_2}, c$

b, d, BMP, a, d, z_{-1} , e, e, g, a, g, a b, d, BMP, a, d, z_{-1} , e, e, g, a, g, a S_{ζ} ad1, 5, a, d 8 (Ba ba a e, a, 1999; Da d e, a, 2007; Sc e, e, e, a, 2007).

I aç a, f, e e d g, ge e e ad , defeç, f, e ea, a d a ç, a, e_{1} (A, e_{2} e a. 2000; S e, e, e e a. 2003). I, e e, ge f_{1} , f_{2} (A, e_{2}), f_{3} (A, e_{2}), f_{3} (A, e_{3}), f_{4} (A, e_{3}), f_{4} (A, e_{4}), f_{4}), f_{4} (A, e_{4}), f_{4} (A, e_{4}), f_{4}), $f_$

BMP and Activin Membrane-Bound Inhibitor

T e_1 , a_1 , ζ e_{ζ} b, a_1 , e_2 , ecc. BMP a_1 d a_2 . $c e_{\zeta} b a e b_{\varepsilon} d , b_{\varepsilon} (BAMBI) a a$ ce, β_1 , β_1 c ca, b, d TGF- β a, d, e $\zeta e_{\zeta} be_{\beta} = f_{\gamma} e^{T}GF-\beta fa_{\zeta} , b_{\gamma} , a_{\gamma} a_{\gamma} a_{\gamma}$, acerera d z a, 1, e, z a c aç, (O, c, c, e, a, 1999; G, e, d e a. 2001; L e a d e a. 2003). BAMBI be e ed, aç a a ega e ega a f BMP ga, g d, g ezb, c de e, z e, (O, c, c, e, a, 1999; T, a, g, e, a, 2000). Beca, e, e e e, f BAMBI, d, ced b TGF- β , ζ a a_{+} ac , a ega e feedbac ζ ec a, ζ , TGF- β , g, a, g (Se a e a). 2004; X e a. 2008). Mec a, , ca, , BAMBI , e g e 1 , S_{ζ} ad7 a, d , b, TGF- β , g-, a, gb f, ζ, ga, e, a, cζ, e1, TβRI a_1 d S_z ad7, e eb , b_1 , g_1 e , e_1 aq , be 1 ee, T β RI a, d R-S₅ ad (Ya, e a. 2009).

Cripto

C, μ , a_{μ} , 1, a, C, -1/FRL-1/C, c(EGF CFC), a GPI-a, c_{μ} , ed $\epsilon_{e_{\lambda}}$ b, e_{μ} , g_{μ} f a EGF- e a d a CFC d ϵ_{λ} a I_{μ} b, d_{μ} , d_{μ} a d_{μ} , $e_{\mu}^{2} \epsilon_{\mu}^{2} \epsilon_{\mu}^{2}$ b, f_{μ} e GDF fa ϵ_{μ} a d fa ϵ_{μ} , $a \epsilon_{\mu}^{2} \epsilon_{\mu}^{2}$ g, d_{μ} , e^{-} a ϵ_{μ} , 1, e ALK-4 a d ALK-7, ece μ (Ya, $\epsilon_{\mu}^{2} a$, 2002). I, add, C, C, μ d, ec eg, $a \epsilon_{\mu}^{2}$ TGF- β , $g_{\mu}^{2} a$, $g_{\mu}^{2} e$, $e_{\mu}^{2} c$, $f_{\mu}^{2} c$, $e_{\mu}^{2} c$, e_{μ}^{2}

GDF, g, a, g, C, r, c, d, a, e, e, g, a, g ac, e, e, f z a, r, e, a, i, a, c, d, g z e, be, f, e EGF, ece, faz, a, d W, faz, f, g, g, g, a z, e, g, ba, e, f, c, c, ece, d, e, e, b, g, ca, ce, e, a, g, g f, z, e, b, c, c, d, e, ce, e, a, g, g f, z, e, b, c, c, d, e, ce, e, a, d, e, c-ce, e, e, a, f, c, a, d, e, c, ce, e, (Naga, a, e, a, 2012).

RGMa, RGMb, and RGMc

Te e_{f_1} e g_{f_2} da $e_{\zeta_{r_1}}$ e g_{r_2} e b_{r_1} f ζ_{r_2} (RGMb; a ca ed DRAGON) a a GPIa, c_{-} , $ed_{s_{-}}$, ec_{e} , e_{s} , b_{-} , d_{-} BMP-2 a, d_{-} 4 a, dfac, a e, g, a, g, a BMP, e II a, d, e I ece $(Sa_z ad e a . 2005)$. $S_e d e , e a$ e, e, a, ce, a e je ea, ed, e, e, a, f RGMb, di, - eg, a e E-cad e , e, e, e -. e, , , a a, , a f, eEMT, e. , ea, d, de ce a , b, be, gie, -e, ab, ed e_{1} , e_{2} , TGF- β (L_s e a 2013). A, e_{2} , RGMb f_{1} , c_{-} , e ac f TGF- β a' e fa \mathbf{r}_{t} ded \mathbf{r}_{t} e $\mathbf{e}_{\mathbf{r}_{t}}$ (L_F e a. 2013). T e RGMb - <--- g RGMa a.-aç a a BMP ç ece , a d fac, a e , e e-, eq. e a c_{a} c a f_{a} f BMP, ga, d f_{a} c_{a} c c_{a} c , e II, ece, , , , , a g' RGMa e , e , , e, e, e, f, Aq RII a, e, g, a, g, ece, e, f BMP-2 a, d BMP-4,1 e ea 1 RGMa e e -, e, e, a, e, a, e, ga, d, , e, e, e, f, BMPRII a, e, g, a, g, ece, (X a e, a. 2007). A , c , ece , f , c , f , BMP a bee, a c bed, RGMc (a, 1, a e- ζ , g, e, β , 1 c a_{ζ} , 2e BMP, g, a, g, , e, e, ead, g, e c d, e - eg, a , a, d a bà a, c', g_{ζ} ec a, ζ f \ldots e a, \ldots ζ e -, a , e b d (Bab, e a. 2006). Acc dg, cara, e RGMc c ece, dec'ea e BMP, g, a, g, e, e, e, e, g, g, r 1 e c d, e e a d g , acc (s, a, , $a_1 c_2 e_1 e_2 c_2 c_3 c_3$

CD109

T e GPI-a, c, ed., e, CD109 be, g, , e α_2 -ζ ac, g, b, faζ, (L, e a. 2002) a, d b, d, TGF-β11, g, afζ, a, d, e, TGF-β, f, ζ, 1, 1 e, afζ, (Taζ e a, 1998). La, f, ζ, a ζ ζ, e 1, TGF-β, g, a, g, ecc., a, d, ega., e, eg., a, e, TGF- β , g, a, g (F, , , , e, a, 2006). CD109 d, ec, , e, ca, a, f, TGF- β , ecc., ca, e, ae a, d, c, e, e, e, deg ada, (B, e, e, a, 2011), a, ce, ce, gS_{\zeta} ad7 a, dS_ζ, f2 (B, e, e, a, 2012).

Neuropilin-1

Ne -1 (NRP1) $a_1, a_1, \zeta \in \zeta$ b a_1 e_1 e_2 e_1 a_2 a_3 a_4 c_5 z_5 a_1 e_2 a_2 a_3 a_4 z_1 e_5 a_1 a_4 z_1 e_5 a_1 a_4 z_1 e_5 a_1 a_6 z_1 e_6 a_1 a_2 a_3 a_1 a_1 a_2 a_1 a_2 a_1 a_2 a_3 a_1 a_2 a_3 a_1 a_1 a_2 a_3 a_1 a_1 a_2 a_3 a_1 a_1 a_2 a_3 a_1 a_2 a_3 a_1 a_2 a_3 a_1 a_1 a_1 a_2 a_3 a_1 a_1 a_2 a_1 a_1 a_1 a_2 a_1 a_1 a_1 a_2 a_1 a_1 a_1 a_2 a_1 a_1 a_1 a_1 a_1 a_2 a_1 a_1

SIGNALING VIA TGF-β RECEPTORS IS MODULATED BY INTERACTIONS WITH OTHER CELL-SURFACE PROTEINS

Vascular Endothelial Cadherin

f TGF- β , e, d, e, a, ce $(\mathbf{R}, \mathbf{d}, \mathbf{e}, \mathbf{a}, \mathbf{e}, \mathbf{a})$.

Occludin

T e e , e a , g , ς , ς , a , r , e , c ς d , e a ς , τ , $T\beta RI a d$, τ , e , c q , a , f a ς , e TGF- β , e e , ς , e e , g , ς , ς , ς , e a d d a , e b , f , e e ς , ς , ς , ς , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q , q

Integrins

T e , eg , ece , faz , $z ez be \alpha \beta 3$, a, c , a, a, d ced b TGF- β g, a, g , g 2b, b a, a d f z a c z , e i , T β RII, c fac, a e ac e ece , c z , e f z a, a d e a ce e a g a g b TGF- β , ead g , e , e eg a, f ce , fe a, (Scaf d e a 2004). I, a z a , ce a , b, d i ea, e ac ae , eg , $\alpha \beta 3, i$ c a, i , BMPRII a , c -, a z c d z a f e a e , e ece , ead g , BMP ece , ac a , a d d i , eaz Sz ad a d E 1/2 MAP , a e g a g a g a , (Z e e a 2013).

CD44

 S_{ζ} , a_{γ} , e a_{b} , e a_{ζ} , e, e a_{β} , a_{γ} , a_{γ} ece , CD44, as be read e. e ed ce f_{ac} , face, f_{ac} , f_{c} , $a \in \langle c, e_1, T\beta RI, T\beta RI, \rangle$ b, g, ded b, e, ..., c, ..., a, cd - ζ a, f CD44, a, b, d, e, e T β RI $_{s}$, a- $\zeta e_{\zeta} b_{z} a_{z} e_{d} \zeta a_{z} (B_{s}, g_{s}, g_{s}, e_{z}, 2002).$ $S_{z_{f_1}a_{f_1}}$, $f_{c_{f_1}a_{f_1}}$, $a_{f_{f_1}a_{f_2}}$, $a_{f_1}a_{f_2}$, $a_{f_2}a_{f_2}$, e CD44 T β RI c , e , e , a ce R-S_c ad, a., a, d CD44, a, ..., a-, b, $eT\beta RI$, 1 c , c, e a, c, gr, e ac, c_r , e, e, e, a, d ζ g a, , e-, e, b, ea, ca, ce, ce, (B, g, g, g, , e a. 2002). O, , e, , e, $a_1^{-}d_2$, $de_{\zeta} a_1 \perp b_2$ ba, , CD441 a fs, d, a e a ega e, e d_{g} , g TGF- β , g, a, g b affec, g TGF- β /ece , e, d c , (P , c e a . 2014). W e e BMP ece $f \neq f \neq c \neq f \neq c \neq c \neq c \neq c \neq c = 1$, CD44 $e_{\zeta} a_{1} e_{\zeta} c_{1} e_{2} e_{2$

Platelet-Derived Growth Factor β

I, de $\langle a \rangle = b$, $b \rangle a_{11}$, $T\beta RI f \langle \zeta \rangle = c_{g} - s_{g}$ face $\langle \zeta \rangle = e \langle e \rangle = 1$, CD44, $b_{11} a_{11} = 1$, $\langle e \rangle = a e e - de \rangle = e d g = 1$, face β ecce $\langle e \rangle$ (PDGFR β) (P $\langle c \rangle = a = 2014$). I, $e \rangle = a \langle e \rangle = g$, PDGF-BB $\langle \zeta = a \rangle = a \langle e \rangle = a \langle e \rangle = a \rangle = f$ $\langle a \rangle = a \langle e \rangle = f \rangle = a \langle a \rangle = a \rangle = a \langle e \rangle = a \rangle = f$ $\langle a \rangle = a \langle e \rangle = f \rangle = a \rangle$

TrkC

 $A_{r,t}$ e, ece r, r, r, e, $a_r e_r$, $a_r, a_r, a_r, 1$, , $e TGF-\beta$, ece_{β} , e_{β} , e_{β} , e_{β} , ece_{β} , ec, e aç e c ç é c ece, Te-T, C, ETV6-NTRK3 (J, e a. 2005, 2007c). B, ETV6-NTRK3 a, d T C a cae_1 , T β RII, $[e_{\mathfrak{s}}, e_{\mathfrak{t}}, e_{\mathfrak{t}}, e_{\mathfrak{t}}] = e_{\mathfrak{t}} e_{\mathfrak{t}}, a_{\mathfrak{t}} d d_{\mathfrak{t}} e_{\mathfrak{s}}, a_{\mathfrak{t}} - e_{\mathfrak{t}} e_{\mathfrak{t}} e_{\mathfrak{t}} - e_{\mathfrak{t}} e_{\mathfrak{t}} e_{\mathfrak{t}} - e_{\mathfrak{t}} e_{\mathfrak{t}} e_{\mathfrak{t}} - e_{\mathfrak{t}} e_{\mathfrak{t}} e_{\mathfrak{t}} e_{\mathfrak{t}} - e_{\mathfrak{t}} e_{\mathfrak{t}}$, e $f \leq a_{1}, 1$, T β RI, $f \leq c$ ed a, g, ega eç, try fTGF-β, g, a, g. T e, ç ge, c $ac_{t}, e_{t}, f_{t}, e_{t}, e_{t},$, e ef e be , c, ed b a, ag , g. . r g ca TGF- β , g, a, g. T e, a_z e z ec a, z ees a , r , e BMP ece, , , a T C b, d, a, d, L, a, e, e BMPRII c, a, ζ cd ζa, ca, gd, gd, f, ecζ, e 1, eBMP, eI, ece, a, d, f, e, f, fBMP, g, a, g, c, ca, ce, ce, (J, e, a). 2007b). H 1 e e , a TGF- β a d BMP g a , g te y serve, be an extended ce in $g e_{A-1}$, $\zeta ec a_{A-1} c' \zeta_{-} de_{A-1} f T C_{-}$, $\zeta =$ ge, e, , a, , e, e, f TGF-β ece_{r} , $g, a, g', f, d be e a_{f} a ed_1$, ce_{r} , a , ca, . . .

Ror2

T e ece $a \in \mathbb{R}$ $2 f \leq c \leq$ e e 1 , BMPRIB/ALK-6, a d ac a , f BMPRIB/ALK-6 b GDF-5 ead a = 1 a , f a = 1 f R 2,1 c t e e e ce BMP

 S_{ζ} ad, $g, a, g, a, d, a_{\zeta}, a, e, E, 1/2 MAP$, a, e, g, a, g, ead, g, c, d, ge, c, d ffe $e, <math>a, c, (Sa_{\zeta}, c, a, e, a, 2004)$. T e_{ζ} ec a, c_{ζ} b_1 c $R, 2 a_{\zeta}, a, e, a, 2004$. T e_{ζ} ec a, c_{ζ} f BMP-, ec $_{\zeta}$ c R- S_{ζ} ad $_{\zeta}$, g, e_{ζ} , e_{ζ} , e_{ζ

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, ζe_1 , ed ab e_2 , $e_{\zeta \zeta \epsilon_1}$. , FKBP12 b, d, , e GS d ζ a, f T β RI, С , b,, e, a e (H, e e a'. 1999). L a ea a, e, a, e, e I, ece f_{i} , e TGF- β n rei e aç e, a, d e, a, b, ed $f_{1,\zeta}$ b $f_{1,\zeta}$ $a_{1,\zeta}$ $c_{1,\zeta}$ $c_{1,\zeta}$ FKBP12. T ζ ec $a_{1,\zeta}$, $c_{1,\varepsilon}$, $e_{2,\varepsilon}$ ed $a_{\zeta_{2,\varepsilon}}$, g_{ζ} , $a_{1,\varepsilon}$, $e_{1,\varepsilon}$ ece, β , e TGF- β fa₅ , a FKBP12 ca a, ega e ega e, e a e a c, e f BMPRIA/ALK-3, Aç RIA/ALK-2, a, d Aç RLI/ ALK-1 (S. e.e., e.e. e. a. 2013). Maran , e c, f, e GS d a, f, e BMP ece , Aç RIA/ALK-2 , e ea e , e , ece , $f_{c} \in FKBP12 c$, $a_{c} d c a_{c} e_{t} c$, $c_{c} e_{t} e_{t} e_{t}$ aç a, ,1 c, a de ce, a, e de g e a grada fiza fied, e a a, d z e, e, c z a ... ge, te, ce, te - te c, e, , a c a aç e, , c, f, e ç, ge, , a, , $d_{r-\zeta} e_{r-\zeta} b_{r-1} d_{r-1} a_{r-1} a_{r$ $(ee f_{1}, e d_{1}c_{1}, be_{1})$ $(e a D_{1}, e)$ e a. 2010; C a _s ad e a. 2012).

Se e_{1} , e_{2} , e_{3} , e_{4} , e_{6} , e_{7} ,

a a T β RI-, e aç g., e, i c g. e ece, g, a g b , ab, g, e b, d, g f S_{ζ} ad7, e ece, (Da, a e a 1998; Da, a a, d M e 2000). STRAP a a bee, e., ed, e a e bee, e, de-de e ed, a e 1 (PDK1), c aç a e A , , T β RI a, d, f, e, e, e, aç a, (Se ge a. 2005), a, d, b, d a, d b, e, e, c, de d a e (NDP) a e NM23-H1 (Se g e a 2007). STRAP, a affeç TGF- β g, a g a e e a c ec a, c, S_{ζ} a, Ye -a, c a ed , e (YAP65) f c, c c, e e 1, T β RI a, d e, a ce ec ec c f c e, f S_{\zeta} ad7 a d ec , e aç a, e a 2002).

A add, a ega e eg a f TGF- β g a g , e ada β f β Da e 2 (D. 2), c b d T β T β T β C b d β T β C β C b β C b β C β C b β C

¹ A $_{\mathcal{H}} \zeta$ be $_{\mathcal{H}} f c_{\mathcal{H}} , a_{\mathcal{L}} c$ ada $_{\mathcal{H}} , a_{\mathcal{L}} d$ c a e e e a c a e $_{\mathcal{H}} c$ a e $_{\mathcal{H}}$ · · · · · e , g, a , g. T e c a e , e . . , e , , H. 90, b, d, \sim T β RII a, d T β RI a, d \sim , eq. $e_{\zeta} f_{-\zeta} a_{-\zeta} c_{-1} , e_{\varsigma} b_{-\varsigma} , ga e$ $S_{\zeta, \varphi}$, $f_{2, \gamma, \varphi}$, ab_{γ} , g, ac_{γ} , e, $ece_{\gamma, \gamma}$, c_{ζ} ee ad. g. g. S. ad. g. a. g. d. 1, f ea_{ζ} f TGF- β (W g , e a 2008). T e ada _____e, TLP (TRAP-1-_e____e) a $c a e_{1}$, T β RII (a, d ac, c, ece c,) a, d 1, S_{ζ} ad4 (Fe c e a 2003). T e e f TLP ee_{ζ} , ecf, ee_{ζ} , ea_{ζ} , a_{τ} , fS_{ζ} ad2/ S_{ζ} ad4 , g, a , g, 1 , e b , a , g S_{ζ} ad3/ S_{ζ} ad4, g, a, g. I, ζ e a, g a, ce, , e HLA-B-a c a ed, a c d (BAT3) ada b b dT β RI T β RII ς , e e a d ..., e, a e S_{ζ} ad g_{q} , g_{q} , g_{a} , d_{ζ} a_{z} - e_{q} e_{d} , e_{d} , e_{d} , e_{d} , TGF- β (K a e a. 2008).

S. $d \in a, -c, a, g \text{ SOCS } b$, e 1 (SPSB1) $b, d, T\beta RII, b, T\beta RI, a, S$ S. $d \in a, (L_{\varphi} \in a, 2015)$ a, d, ega = e $\langle -d_{\varphi}, a \in TGF-\beta, g, a, g, b, ec_{\varphi}, g E3-ga = e() = a, SOCS b, ead, g, -f = b, g, a, a, a, ega = e feedbac, e.$

Cytoplasmic Kinases: cGKI

T e c ç c g a e^{3} , e^{3} , 5^{-2} , a^{-2} , $a^$

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

T e $R_{-} - a_{+} c a_{-} e d_{+} e , e_{+} e , e_{+} a_{-} e$ R c 2, be, 1, f, ..., e, eg, a., f $ce_{H} \in ga_{+}, c_{+}, ac_{+}, ad_{+}, c_{+} edc_{+}$ $e_{e_1}e_{e_2}e_{a_1}e_{a_2}e_{b_1}$, $e_{e_1}-ade_{e_2}e_{e_2}e_{e_2}e_{e_2}$, , ega e egg a e TGF-β g, a, g af e a $z \in a_1, 1, T\beta RI a_1 d_2, \zeta, g_1 f_ece_{r_1}$ deg ada, , , , , , , , , , , , (Z a, g e, a, 2009b). T ζ ec a ζ a bee 1 be ζ $a_1, a_2, d_2, g_2, e_2, b_2, g_2, e_3, T e_{z_1, e_2}$ e, d, e, g, c a, z 23-1 a bee, 1, b, d T β RII a, d_{z} be 1, a ed af e TGF- β , $\zeta_{\mathfrak{F}}$, $\mathfrak{q}_{\mathfrak{F}}$, (Ta, g e q. 2002). ζ 23-1 , ζ , e, b, S ζ ad-de e, de, (J, e a. 2007a) a d S_{ζ} ad-, de e de, (J, e, a). 2012) g_{a} , g_{c} I, c_{a} , a_{a} , $e_{\zeta - \xi - \xi - \xi}$, e_{ζ} d, e, g, ca, Tçe 2βa, caeı, e , c, a, c, a, fe, dg, e, d, e, a, ce a, d_1 , T β RII a, dbe ag ca e, d, e-da a d, e ce, e e, d, g, ega e egf TGF- β g, a , g (Me, g e, a . 2006).

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

A₁ \neq g , e TGF- β fa₂ , ece , ζ a₁ ca e , e , a ζ a ζ e b a e a d , ace ce b a e (ece , e , e d c, c e ce), e a e bee, e , ed , e a c i , e e, ed , e e ce , T , e a c e ed f, c , e e, ed , e e ce , T , e e c f ece , b e a , e e ce , f TGF- β fa₂ , ece , f, c , b ζ ce , e , f TGF- β fa₂ , ece , f, c , b ζ ce , e , f TGF- β fa₂ , ece , f, c , b ζ ce , e , f TGF- β fa₂ , ece , a, d, a, bee, e, ab, ed f, \cdot , e, g, a, g, a, 1, a, ,, c, d, g, , e, fe, ,, ece, \cdot , ... T e a, e, a, e, ce, a, , 1, c, \cdot , e, c, ea age, f , e T β RI c, \cdot , a, c, c, d, c, a, a, d, \cdot , a, \cdot , ca, \cdot , \cdot , e, c, e, , i, \cdot , bed, c, ... ed, a, e.

Transcriptional Cofactors: MED12 and c-Ski

c-S , a, f e, f ed ξ , a_{11} , f ξ ea_{12} , f e, a ca, a_{12} be, e e, f ec f, a_{23} , a_{23} , $1 e e_{1}$, g, e e, TGF- β , g, a, gb b, d, g f T β RI (Fe, a, d e, a, 2010). T e, e eq. be_1 ee, c-S a, d T β RI \dots f e, f e, a c, f e, f f e, a_{12} , e, f R-S₂ ad/S₂ ad4 c, f e, e f e, e ec, f, f eb, e, g, e d, a_{14} , ff e, e e, f e, f e, f e, g, f e, f e,

TGF-β SIGNALING IS MODULATED BY FEEDBACK MECHANISMS

TGF- β , g, a, g, ca efficient, construction with the equation of the equatio

TGF-β-, d, ced e ..., f TGF-β-, ζ. ga ed c, e 22 (TSC22), 1 c c ζ. g e 1, S_ζ ad7 f, b, d, g, TβRI (Ya, e a, 2011).

 S_{ζ} ad7 b, d, a, d, b, e, e, a, a, , e I ece , , e TGF- β faz , 1 e ea , $\sum_{i=1}^{n} e_i = \sum_{i=1}^{n} e_i = S_{\zeta} ad\delta_{i} = 1$, $\sum_{i=1}^{n} e_i e_i = e_{\zeta} a_i b_i d_i g_i$ a, d, b, aç, , 1 a, d, e BMP, e I ece , ALK-3 a, d ALK-6 (G , e a . 2007). \mathbb{B}_{t} , \mathbb{b}_{t} , \mathbb{S}_{ζ} ad \mathcal{C}_{τ} , e_{z} a e_{z} , e_{z} , e_{z} . , g, e, g ca BMP, g, a, g d, g d ffe en a ... fz e e, c z a ... ge, e, cente , e b a, (Maeda e a. 2004). T a e, - a a a, d a, d d eq, $d_{g}q_{eq}$, fS_{g} ad6 e e_{i} , b_{i} , e_{i} , a_{i} BMP, c_{i} , f_{i} r 1 ed b ac a, fa, c, e TGF-β, g, a g_{1} c, e, d_{c} ce a ec, d_{1} a e fS_{ζ} ad7 e., e, , , , a, , ge, e, 1, , e., ee, , g S_{ζ} ad6, ε_{1} , d_{1} , BMP, ece, a_{ζ} , a_{ζ} , a_{ζ} , a_{ζ} ζ_{τ} , $e_{\mathcal{A}}$, $a_{\mathcal{A}}$, $e_{\mathcal{A}}$, $e_{\mathcal{A}}$, $d_{\mathcal{A}}$, $d_{\mathcal{A}}$, $e_{\mathcal{A}}$, $e_{\mathcal{A}}$, $e_{\mathcal{A}}$, fd ffe e, a, , , e b a, (Maeda e a. 2004). BMP , g, a , g , d ce S_{ζ} ad6 e , e -ce t (I da e a 2000). S c ece t d_1 , $-eg_1a_2$, b_1 , b_{r} , S_{ζ} ad ζa_{ζ} , $-eg_1a_2$, b_r , a_r, $b_$ $b_{1}, e_{2}, e_{3}, e_{4}, f_{1}, e_{1}, e_{2}, e_{2}, e_{2}, e_{3}, e_{4}, e_{5}, e_{5},$ O_1 , e_2 , e_3 a, d_1S_2 ad6 a bee, 1, be ζq , a ed b, $e \zeta q$, a_{χ} fe a e PRMT1 $(X_{r}, e', a, 2013)$. PRMT1 b_r, d_r, e_r, e II ece_{k} , ce_{k} , ae_{k} , ad6, 1, c, be_{k} , d_{k} , e, e I ece , , af e ga, d-, de ced e, e, c, e, c, c, c, c, c, c, c, T, c, a, T, T ζ_{-} d₂ ca₋, f S_{ζ} ad6, e ea e, e BMP, e I ece f_{r} , f_{r} , f_{r} , e, ega e c, f_{r} , f S_z ad6 a, d a, 1, , e I, ece, e , e . . . BMP¹ ec $_{\angle}$ c R-S_{ζ} ad (X_{ξ} e a 2013). T² e_z, , e feedbac , d c_{-} , f S_{ζ} ad6 (S_{ζ} ad7) e e, b BMP ($TGF-\beta$), g, a, g a, d ca e, e, ece, , , , ee, ab, , , ead -, a e, ece f_r f_r $1 - f_r$ a_c a_i a_i .

TGF- β_{1} (ξ_{1} , a_{1} , a_{2} , d_{1} ce, ee, ee, e_{1} , f_{1} e, e_{1} , e_{1} , e_{1} , e_{1} , e_{2} , a_{2} , a_{2} , a_{1} , a_{2} , $a_$

SIGNALING VIA SMAD AND NON-SMAD PATHWAYS

Af e TβRII-, d ced , a, a, d ac-, a_{-} , $f T\beta RI$, $T\beta RI$, a_{-} a, d 3, , e, ca, b, $-\frac{1}{2}e_{\zeta}$, a, SSXS ζ_{r} , f, (Abd , a e a. 1997; S c e , e a. 1997). T e I jece f as f as d , da, , a e S_{ζ} ad2 a, d 3, 1 e ea , e BMP, e I ece, ALK-2, -3, a, d -6, efe e, a, a_{1} , a_{2} e S_z ad1, 5, a_{1} d 8. ALK-1 $a_{1}^{\prime\prime}$ e I ece f, f, $TGF-\beta$, b, a, b, d (e.g., BMP-9 a, d 10) (Da de a. 2007) a, d. a e S_{ζ} ad1, 5, a d 8 (G $_{\varsigma \zeta}$ a e a 2003). $H_1 e e_{\mathcal{H}} e_{\mathcal{L}} e_{\mathcal{L}} e_{\mathcal{L}} c_{\mathcal{L}} + R-S_{\zeta} ad_{\mathcal{L}} + \dots +$ a_{-} , a_{-} , ab_{-r^2} , e, a, d TGF- β a bee, ae a Szadla, d 5 $(L_{s} e a. 1998)$, a T β RI $(L_{s} e a. 2009b;$ W g , e a. 2009b), ALK-2 a d ALK-3 (Da e a. 2008).

T e e , e , e, e I ece, f, e faz , a , e , b ef , e e e c , e L45, f, e , a e d z a , i c b d , , e L3, a d, e ad ace, α - e 1 , e ca b , e z , a MH2 d z a , f Sz ad (Fe g a d De , c 1997; L e a 1998). T e b d g , a b, ed b , e ac , bei ee , e , e , a ed GS d z a , f TBRI a d Sz ad; i e e, e f, e g z , e a , f, e GS d z a , bei ee, e e e, e I ece, f, e g a c , e e e, e e , e , f, e GS d z a , bei ee, e e , e , e e , f, e g z , e e , e e , f, e e f, e e e e e e e e e e e

W e ea, e S_c ad. a 1 a a e f c_s c a $\zeta_{--,\tau}$ a ce f TGF- β g a g, g, e e a e a \ldots $-S_c$ ad g a g a g a 1 a \ldots a ed b τ e a c a ed TGF- β ece \ldots ζ_c d g, e E 1/2, JNK a, d. 38 MAP , a e , a , a , PI3- , a e, a, d S c a, d R. GTPa e $(M_{S,1}, a - a, a, d + e d, 2005)$.

O, e ζ ec a, ζ 1 e eb TGF- β , ζ e, a-, ca, aç a e, e E 1/2 MAP , a e a ecent entre eada , S contra e - -, a ed e d e , $T\beta RI$, a de c bed ab e. Teada, Gb2, c_{ζ} , e_1 , S_1 , a_{ς} çe, dee c a ge, e, f, Ra, ca, e, b, d e, e, e, e, a ed e d e, S c, a d , e aç a ed Ra ç éd a e aç a, f, e $E_{1/2}$ MAP , a e a 1 a (Lee e a 2007). Ac a_{τ} , $f \in 1/2$ d_1 , ea_{ζ} , f'_{τ} , ea e ece a e bee, 1, 6 c ed a e a $g_{-1}, \ldots, z_{+}, a_{+}, a_{+}, d_{+} a_{+}, a_{+$, e_{ζ} , ge_{ζ} ceffe ζ , fTGF- β , ee, ce_{τ} , a, ce_{τ} , e.A., bee, a, a, f, ed ffee, ef c e, c , TGF- β -, d ced E 1/2 MAP -, a e aç a_{τ} , ca_z e f_{τ} z_{τ} , e a_{τ} f TGF- β $g, a, g, de_{\zeta} a \cdot e_{\mathcal{F}}$, $e_{\zeta} de_{\zeta} a \cdot e_{\mathcal{F}}$. I, de ζ a ce, 1 e e T β RII e e a e g , TGF- β efz c e₁²² ac - a ed E $\frac{1}{2}$, 1 e ea , e de c a ce 1, 1 e e f T β RII, E 1/2 ac a 1 a ac a b, ed; a, 2 c a e -. e f T β RII e de c a ce 1 c e d , e e ce, E 1/2 aç a, , , e, , e TGF- β , $\zeta_{\mathfrak{s}}$, $\mathfrak{q}_{\mathfrak{s}}$, (Ba, $\mathfrak{d}_{\mathfrak{s}}$ ad a e a. 2011). I, $f = \frac{1}{2} d$, ac a_{-} , $f = \frac{1}{2} MAP$, a e1 a f_s , d, be T β RI-, de e, de, .

F, e e a, $-S_{\zeta} ad$, a + a, $e_{\varsigma} b_{\zeta}$ g_1 , g_2 , g_4 , g_{12} , g_{22} , $g_{$ c a ed faç 6 (TRAF6) a a c c a e. T e e ac, e, b, d, g_{ζ} , ff, TRAF6, e f_{f} , a_{ζ} , e_{ζ} , b_{z} , a_{z} , e_{z} , a_{z} , $fT\beta RI$, a_{z} , e_{z} , a_{z} , ALK-6 ($\S_{1}, e_{1}, e_{1}, 2008$). TGF- β_{1}^{2} (\S_{2}, q_{2}, q_{3}). e, a, ce, eb, d, g, f TRAF6, TβRI a, d a e-, de e, de, , , a, e. T e aç a ed TRAF6 , e, s, b, s, a, e, e MAP-, a, e, a, e -, a e TGF- β ac a ed , a e 1 (TAK1), ead, g $a_{1} a_{2} a_{2} a_{1}$, (§ $e_{1} e_{2} e_{3}$, 2008; Yaz a-, a e, a. 2008; K , e, a. 2009). TAK1, e, a e a d aç a e, e MAP, a e a e (MKK) 3, 6, 1 c aç a e, e. 38 MAP b, $d_{z} = S_{\zeta} a d7_{z1}^{\prime \prime}$ c ac a a caff d, g = -, e, b, g, g, e, a, e, c, e, eac', e, a, d c_{μ} , e_{μ} , $T\beta RI$, $e_{\mu}eb_{\mu}$ fac, a_{μ} , g TGF- β -, -

d a f TGF- β -, d ced a d EMT. A_{r} , e_{ζ} e_{ζ} be_{z} f, e TRAF fa_{ζ} , (.e., TRAF4), a a bee, c ca ed , e ac a-, f TAKI (Z a, g e a. 2013a). A TAKI gag g , ced, TRAF4 s & s, ae $S_{\zeta,\varsigma}$ f2 a, d \ldots $\zeta_{r,\tau}$ e $e_{\zeta,\tau,\zeta}$ e, τ_{ζ} e, τ_{τ} f, e USP15 de β_{s} , a e, ca, g T β RI, ab, a-, a, d e, a, ced TGF- β , g, a, g (Z a, g e, a. 2013a). A, add, ..., a, b, s, ,, ga e, X-, ed , b_{r} , fa_{r} , $(XIAP)a_{r}$, cae_{r} i, , e TβRI, b ea, ca, ce, ce,, a, d., ζ., e s b s, a, f TAK1,1 č, e, aς -- a, e, , ç, ea, fáç, , кВ (NF-кВ), a, c, , , a aç, (Ne, e, a. 2009). XIAP e, a, ce, b, $S_{\zeta} ad2/3 a d TAK1/NF-\kappa B g a g a d c$ $b_{i}, e_{i}, \dots, z \in a_{i}, a \in e_{i}, b_{i}, e_{i}, TGF-\beta.$

I, add, ,, TRAF6 a bee, , , 1, , be , ed , TGF- β -, d_{β} ced , a_{ζ} e_{ζ} b, a_{γ} e c ea age, f T β RI, e_{f_1} , g_{f_1} , e_{f_2} , e_{f_3} , e_{f_4} , $ace_{r^{\alpha}}a d < a_{\gamma}$, $c_{\gamma}e_{\gamma}$, $a_{\gamma}r$, $c_{\alpha}ed$ $g_{a_{\zeta}}$ (M_g e a. 2011). F , TGF- β - z, e, e aç a, f, ez e ar , e, a e ADAM17 (a ca ed TACE), a TRAF6- a d , e, , a e C (PKC) ζ-de e, de, ζ a, e, 1 c $e_{\mathcal{R}_{1}}$, c ea age f T β RI $e_{\mathcal{R}_{1}}$, de a d'_c a, (L_s e a. 2009a; M_s e a. 2011); e jeza, g.azazezbae azacedaz f , e ece p_{1} , e bec ζ e q_{1} , ce p_{2} e q_{3} ad d_{1+} , a ç ea age b γ -, ec e a e γ , e , a, - $\zeta e_{\zeta} b_{\alpha} a_{\alpha} e_{\alpha} e_{\beta} e_{\alpha} e_$ r, a d < a, (G, de e, a. 2014).

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f TGF- β ece β (W₄ a d De β 2009), f c ca be ζ b ed β ee β a β 2009), f c ca be ζ b ed β c a β e β a β a β e ce β face b A β - β ced β a β

ae, ecab, a, f Ke, e, c, a, , -de, e, e TGF-β' ece 👝 ç ζ -). TβRII ą, b,d, e e, -, , g, , e, 26 -, de, e, de, , , a, , e;; , d, be fcsca < ce , , , , ec c , g a d f , e, e a ce_n (Y, e a.

, e, a a, · aça , -, e Sz ad g, a, g, ca, be , e , a ed a d ae, -caedeçe, 1 c'., ece , deg ada , (F g. 3) (Ra a, a. 2001). T _ , g , _ , a , a , TGF-β e $e_{ac_1} e_{ac_2} e_{ac_3} ad7/S_{c_5} f_{2_5} b_{-}$

ce

s, a, c, e a, d a e deg aded, -----, ea z e a d z e (D G g e z 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, c, a, de e de, , , ç a , -, de e de, , c ec a-, , , (F, ge, e, a. 2008). C, a , , - , de e, de, , e, a a, f be ag ca, eez, be f_{s} , edf f_{s} eff c e, ac a_{s} , fb, S_{ζ} ad2 a d. 38 MAP , a e , a , P - , a , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β - , β . . . e, ea, ca, f, e, caff, d, g. - f_{i} , f_{i} , d_{i} , a_{i} , d_{i} , c_{i} , e_{i} , e_{i} , d_{i} , c_{i} , cf be ag 'ca, (C e, e a. 2003). T β RII 1 a $f_{\mathfrak{s}}, d_{\mathfrak{s}}$ b, $d_{\mathfrak{s}}$ e, $a_{\mathfrak{s}} \in b$ a, $e_{\mathfrak{s}} \in a_{\mathfrak{s}}$ -, e, a e ADAM12, 1 c, , a ..., ea e-, dee de, ζ a e, z, z, e z, g f T β RII , ea, e, d, z, e, c, z, e, e, 1, , b, d, g \sim S_z ad7, a, d, e eb \sim e e, \sim deg ada, (A, β e a. 2007). C γ e TGF- β ece γ , e, a, a, ca, a, be, eg, a ed b, e deg ee, f N_{-} , ed g c, a, f, e, ece, (Pa, dge e a. 2004). T e β 1,6-N-ace $-g_{f}$ -, , a, , -, eg, a, ed, , , a, ca, ce, a, dg c_{μ} , $a_{\mu}e_{\mu}$, e_{μ} TGF- β_{μ} ece $e_{\mu}e_{\mu}$, $ead_{\mu}g_{\mu}e_{\mu}$ ged e de ce f, e ece i , e ce face.

 \mathbb{B} , $T\beta RI$ a, d $T\beta RII$ 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, -

aea de f TβRII de e de, a LTA VA F_{ζ} , fbe₁ ee, a_{ζ} , acd e d e $529 a, d538, e, e, e, e, (M_{e}, e, a, 2007).$ Be ag ca, a, ca, ca, e, e, ba, a e a, a, f_{1} f_{2} f_{3} e_{1} f_{3} e_{2} f_{3} e_{2 , a., f P. 826, e. , c. , a. c. d. - ζa_1 , f_1 , ece, ζa_1 , ed_1 , fc_1 , fc_2 , a_3 , a, d, d, ç, , f EMT (Me'e, e, a. 2014).

MUTATIONS OF SERINE/THREONINE KINASE RECEPTOR GENES IN DISEASES

 $M_{g_1}a_{f_1}$, ge, e, e, c, d, g ζ e ζ be f_1 e $e, e', e', e, e, a, e', ece_{tr}, fa_{\zeta}$ a e bee, b_{e_1} ed a_{e_2} be fd ffe e, d_{e_1} ea e.

Malignancies

I, aç a, $g_{\zeta \in I}$, a_{I} , e TGFBR2 ge, e a e $\varphi_{\zeta\zeta}$, e_{ζ} , e_{ζ} , b_{α} , e_{ζ} , b_{α} , e_{ζ} , b_{α} , de, ead, a, d, ec, ζ_{i} , g_i , a, TGF- β_i , g-, a, g, e, e, a, z, ,, a, 1, 1, z, z, , -, e, , e, e e, ee, ee, Ka, d, ea. 2013). I, -, e, e, , g, $\zeta_{\mathfrak{F}}$, $\mathfrak{q}_{\mathfrak{F}}$, TGF- β , ece, β , ge, e a $e_{\zeta \in C}$, e_i , $c_{\zeta \subset \zeta}$, f_i , $e_{a_{\zeta i}}$, e_{b} , $b_{ea_{\zeta i}}$ ca, ce, a, d, e_{1} , e_{2} , a, Ca, ce, de e_{1} , e_{1} , e_{2} , e_{3} , e_{2} , e_{3} , e_{2} , e_{3} , e, e, a e, e, e, e, e, e, e, f, e be, -c a aç é ed e a_{ζ} , e_{τ} , $f_{\tau \in \zeta_{\tau}}$, e_{τ} . f, c, f TGF-β a, d BMP, g, a, g. T e ge, e-e, c d, g TβRII f'e e, e, , se, a ed (30% fa, ca, e), c, eça ca, ce a $e_{1,7}$ (B₁ a e a 2008). A c a aç e , c s bç a f ç, eça ç a g, a, c, , 1, a, ç ç, a e, e $\int_{\mathcal{A}} ab e (MSI)_{\mathcal{A}} \zeta_{\mathcal{A}} , a, d, \int_{\mathcal{A}} c ca e \int_{\mathcal{A}} e$ ge, ee, ç d, g TβRII (s, a edi, af'e, e, c f g e , a 90%. $MSI_{15} \leq a$ e defec-, ez zac e a zac e e, a f'e e, ead, e, ca, e, , e, ec a, 1 e, e DNA 'e e ce c , a , g , e c e f ade-, e-, , , d, e-ba ed de , ç ç e, de. E_{-} , 3_{-} f, e TGFBR2 ge, e c, a, al., ade- $, e_1 a \zeta, a_{1} \zeta_{\mathfrak{s}_1} a e d a d_1 c a bee$ $c_{a_1} \ge ed_{a_1}$, $e_{BAT-RII} \le a_1$, ece_{a_2} , ge_{a_1} , ge_{a_2} , ge_{a_2} , ge_{a_1} , ge_{a_2} , ge_{a_2} , ge_{a_2} , ge_{a_2} , ge_{a_2} , ge_{a_3} , ge_{a_4} , gejes, g, faze, fzsta, , a e, c de , et as e, e, t, a ed, ... e, 1., d, ..., ca ed <u>s</u>, a, ece (B, 1 a e a. 2008). I, -, e, e, g, e de e, z e, f, c z, a, TGF- β ece , a bee, ed , e. f_{ζ} , e_{ζ} , b_{α} , f_{α} , f_{α} , e_{ζ} , ab_{β} , e_{g} , b_{α} , e_{ζ} , b_{α} ,

 ζ c_r ca_r, a, d a_r, e_r, e_r e_r, ce_r, a $e_{1,1} = a_{1,2} = 1$, $e_{1,1} = a_{1,2} = e_{1,2} =$ fe a e g a f TGF- β (B a e a 2008). N_{1} , $T\beta RII b_{1}$, a_{1} , $T\beta RI ca_{1}$, ffe_{1} , c_{1} $[\zeta, a] = e_{\zeta, \epsilon_1} ab e_{-} ade_{-} e_{-} ac ca_{-} ed$ b $\zeta_{1,\zeta}$ a c e a defec, a d, $e_{\zeta,\xi,\tau}$ a, aee, 1, a TβRI6A a bee,, ed jed, e, c, c, ca, ce, 1, a f'e, e, c, f 100%; <u>1</u> e e, ca ef, e az , a., f c ... f_{c} , ca, ce, a_{c} , ca, $ga_{\zeta_{s}}a_{\tau}$, a, 1 e e e c cra, a e car a e (Ba, e, a. 2005). A, e, e, f, e, -, a , a g a, c, e e ed, a c, jeçà ca, ce, a d e, , de e, d', c, -¿ a c , e a, defeç,, 1, 5, a, , e BMPR1A/ALK3 ge, e; ge, e, c, c, ee, , g f $ca_1, c_2, f fa_2, e_1, ge_ea_g ca_g$ e_{1} , e_{2} , e_{1} , e_{2} , e_{3} , e_{4} , e_{5} , e_{6} , e_{6} , e_{7} , e2011).

N₁, c, eq a ca ce de e d, gee c, ed , , a ζ a

Juvenile Polyposis Syndrome

. e, d . . , e ba a, ced aç . , . f , e PI3- a e/A, a e, 1 c, e, de, e c, e, f, e., a a e PTEN. I, , e ef e, ,vg, g, a JPS a e, , e, , a e, e a centra e gene e, ç d, g BMPRIA/ALK-3, S_{ζ} ad4, a, d PTEN, de e , g defeç e BMP a 1 a a d e e aç e z ba a, ced, e_z -ce, d_z c_z , a_z , c_z , e_z . e_z , a_z , c_g , f_z (He e, a_z , 2004). F_z z a nee, g , a .. ec 2 c z z a ..., a accz z z a e .. e BMPR1A/ALK3 ge, e ζ a , e eg, e ζ d-, g, ee, acere, a d < a, b, , , e, ga, db, d, g, e face f, e ece, (K, c e a. 2008). T_f, f_{f} , f_{f} , g_{f} , $eALK-3ge, e_{\zeta, \varepsilon}, a_{z}$, affeç, eg, ba, f, d-, g. f. e ec. d (a , f.) ece , , , f. ζ a , g, e ζ f a, i, e, a a, i e, e, ... gca aç, fBMP, e, e, a c c e, g JPS a e a ed ab e.

Hereditary Hemorrhagic Telangiectasia

He ed, a e_{ζ} , $g = a_{\zeta} g = c_{\zeta} a_{\zeta} a_{\zeta} (HHT)$, a, a, , , , , a, , a, c, a, d, , de, 1 c cajace edb c c c a a e e a geçae ada, e e e zafza, i. I a bee, 1, a e e ge (e a. , e ge, e f e, d g , a, d ALK-1 ca, e HHT1 a d HHT2, e eç e (McA, e ę ą. 1994; J 🚬 ę ą. 1996; Abdą a'ę ą. 2005). Teebea, gge, aë, dg, a, dALK-1, eae, ea_cega, ga -1 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, 1 a, f, d, be , de e, de, f T β RII, e ga, d , e ed ε, e, be a TGF-β f, f, c; b, BMP-9. BMP-10 a e, $e_{\zeta_{1}}, \zeta_{2}, a_{1}, a_{2}$, a, fALK-1, (Pa e a. 2008).

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2012).

 $L_1 \subset e_{r_1} e_{q_1} a_1 e_{q_2} , b_{r_1} f_r e$ TGF- β ece $\frac{1}{2}$, $\frac{1}{2}$ $fTGF-\beta$, b_{r} , $Teec_{r}$, d_{r} , fe_{r} ç_c, e_{e1}, b, d, g, fATP, , eATP-b, d g_{i} , e_{i} , f_{i} , e_{i} , a_{i} , e_{i} , a_{i} , d_{i} , e_{i} , a_{i} , f_{i} , e_{i} , b_{i} , eTβRI , a e e eç e , b , f e, a , b-, e aç , e I ece ALK-4 a d, e da, e I, ece. ALK-7 (Y, g, ge, a. 2004). $T\beta RI$, a e, b, a e bee, 1, , a, $z a_{\zeta} de_{a_{\zeta}} de_{a_{\zeta}} b_{\zeta} a_{\zeta} a_{\zeta} a_{\zeta} dz e_{a_{\zeta}} a_{\zeta}$ $f, f = a_{\zeta}, e, b = a_{\zeta}, ca, ce = ce_{H}$ (Ba, d_{+} ada ę ą. 2006; Ge ę ą. 2006; E ą a ę ą. 2007; L_s e a 2012), ζ e a ζ a ce (M $a_{\zeta \zeta}$ ad e a. 2011), g _ z a ce, (U , e a. 2004; Z a, g e a. 2011), a d z e, e, z a ce, (S s e a'. 2007). T e effec f_t e b_{t-1} , c_{f} de b_{1} , f_{ζ} e, e, c, ζ a, a_{1} , a_{1} , f_{1} , e_{1} , e_{1} , e_{2} , e_{1} , f_{2} , f_{3} , f_{4} , f_{5} , f_{5 <-, ce, , aç , a, , f, e , (e, , e, , e, , b, fa, g, ge, e, ., b, f, e, e e, gb, ez e a, a , a, d, za å, fisce, c, ca d, e $e_{ca}a_{+}$, $a_{+}a_{+}a_{+}$, $e_{+}T\beta RI$, $a_{+}e_{+}b_{+}$, LY2157299 ζ_{-} , d a e (a, , a c ed gas, -e, b), ed, be ef, cac, aga, ζ_{-} aga, ζ_{-} aga , a, g, (R, d, e, a, 2015a,b). P, e , $a_{1,\zeta} a_{1,\zeta} e_{1,\zeta} e_{1$, de effec, $f T\beta RI$, a e, b_{r} , j = 1 e e, $c_a d_{a_1} c_1 a_1 e_2 ded a_1 a_1 e_{a_1} e_1 e_1$ ed1, gas, e, b, ..., d, g, s, ..., f, e \dots b, , , , a, a, , -TGF- β d, g ca, be c, $ca_{1} \in ef_{1}$ (K ac e a 2015).

CONCLUDING REMARKS

T $e_{1,\mathcal{F}} c_{\mathcal{F}}$ a a d f $c_{\mathcal{F}}$ a $\ldots e_{t} e_{t} e_{t}$ f e_{t} ece $\ldots f$ TGF- β fa $c_{\mathcal{F}}$ $c_{\mathcal{F}}$ be a ebee c a ace edd $g_{\mathcal{F}}$ $g_{\mathcal{F}}$ $e_{\mathcal{A}}$ 20 ea . We $\ldots 1$ a e $g_{\mathcal{F}}$ $g_{\mathcal{F}}$ $e_{\mathcal{F}}$ $e_{\mathcal{F}}$ e

W₁ : ega d₁. T β RI a d T β RII, 1 e , 1 , a, e e ece, ... a e ca ef₁, c, ... μ ed b ... μ , a, μ a , a ζ_{-} d₂ ca, μ , a d₁ a , e e d c, ... a d, μ ace β_{1} a , ... g a e ζ_{6} c a f, e, g, g, g, E, a, g, f, e, 1

W_t, e a ζ f_t, ea , g d, ea e, 1 c TGF-β, g, a, g, ... e aζ e, ζ_f d, g ada, ced ca, ce, , TGF-β, g, a, g, ece, ... a e bee, a ge ed 1, ... ζ e e, ζ_f ag, g, e- F_{1} , F_{1} , e_{1} , e_{1} , f_{2} , e_{1} , f_{3} , e_{1} , f_{3} , e_{1} , f_{3} , e_{1} , f_{3} , f_{3} , e_{1} , f_{3} ,

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We, a, I, gega d Sc , e f , ec e a a a ...-, a, ce, a, d a, a_t a, $d \stackrel{\sim}{,} e_t e_t e_t$ be $f_t e_t$ $e_1 e_2 c_1 c_1 = e_2 a_1 a_2 g_1 c_2 g_1 ab-$, a, .T, a, ce e c a e i, f c a , a ge, e < be, f. e b, ed. a e, ; 1 e e, beca, e, f, ace, c, a, , i e a e bee, f, ab, e , c, de a, je e a, , , b, ca, , , , , , d, c_{1} , We a g e_{1} , e_{2} , e_{3} , e_{1} , e_{2} $e e a_{1} a_{1}$, bee, $c_{e} ded_{1}$, ee a, c, e. We ac , 1, edge f, d, g b, e If di gI, in the eff Ca, ce Re ea c , e Si ed-Ca, ce, § ce, , e Sied, Re, ea, c C, , $c_{1,1}$, $e \operatorname{Ne}_{1,2}$, $f E ce_{1,1} e$, $ce_{1,2} E \operatorname{NFIN}_{s}$, $de_{1,2}$, $e E_{e}$, $ea_{e} U_{e}$, FP6, $g a_{\zeta}$, $a_{e} d_{e} e I_{e}$ -, a Ta, g Ne1, IT-Le, de, eE, - \therefore ea, U, \therefore FP7. \therefore g a_{ζ}.

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