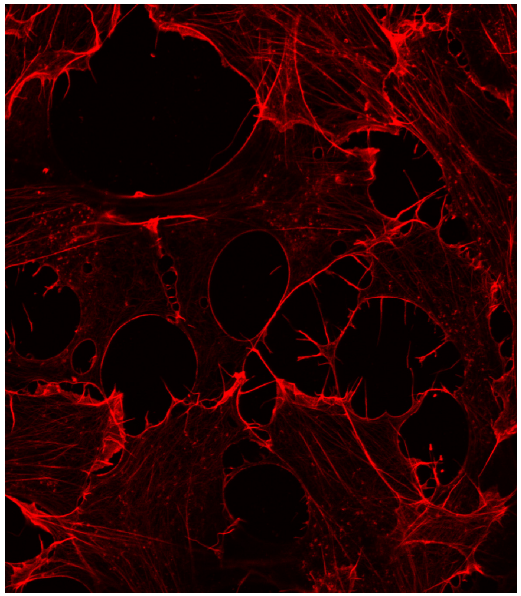
Smad-dependent and independent signalling in osteoblast biology



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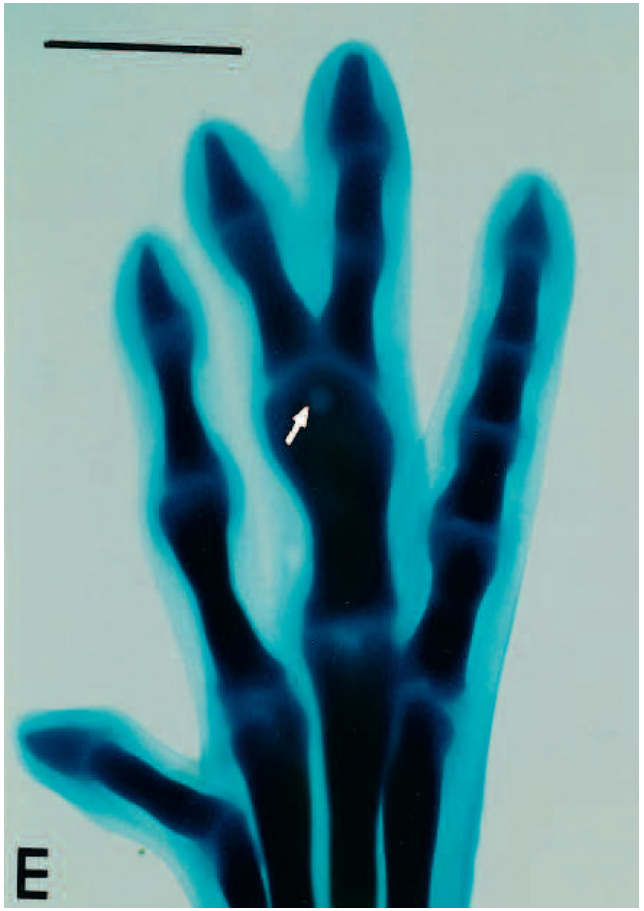
INSTITUT D'INVESTIGACIÓ BIOMÈDICA DE BELLVITGE

BMP-2 regulation of osteoblast biology

- Transcriptional responses mediated by Smad-dependent signaling.
- Transcriptional responses mediated by Smad-independent signaling.
- Cooperativity between both types of signaling pathways .
- Smad-independent effects involved in regulation of cell migration and cytoskeletal reorganization.

BMP regulates skeletal development

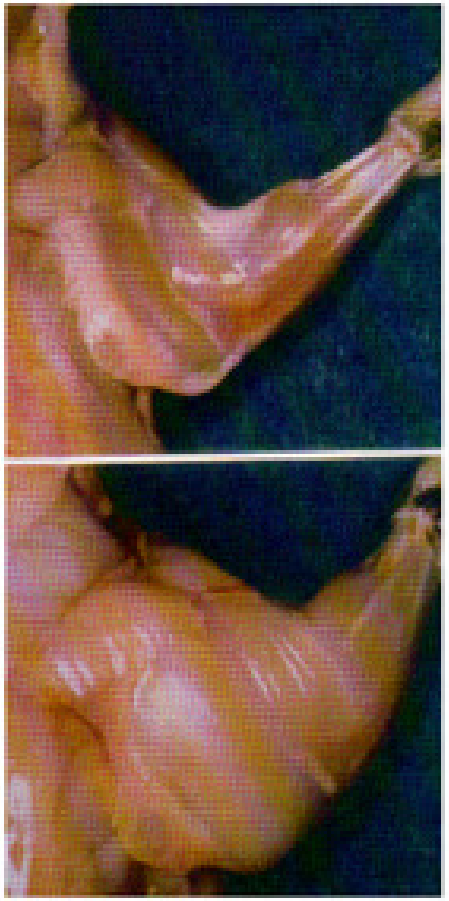


+ BMP-4

Gañan Y, Macias D, Duterque M, Ros MA, Hurle JM.
Development (1996)122:2349-57

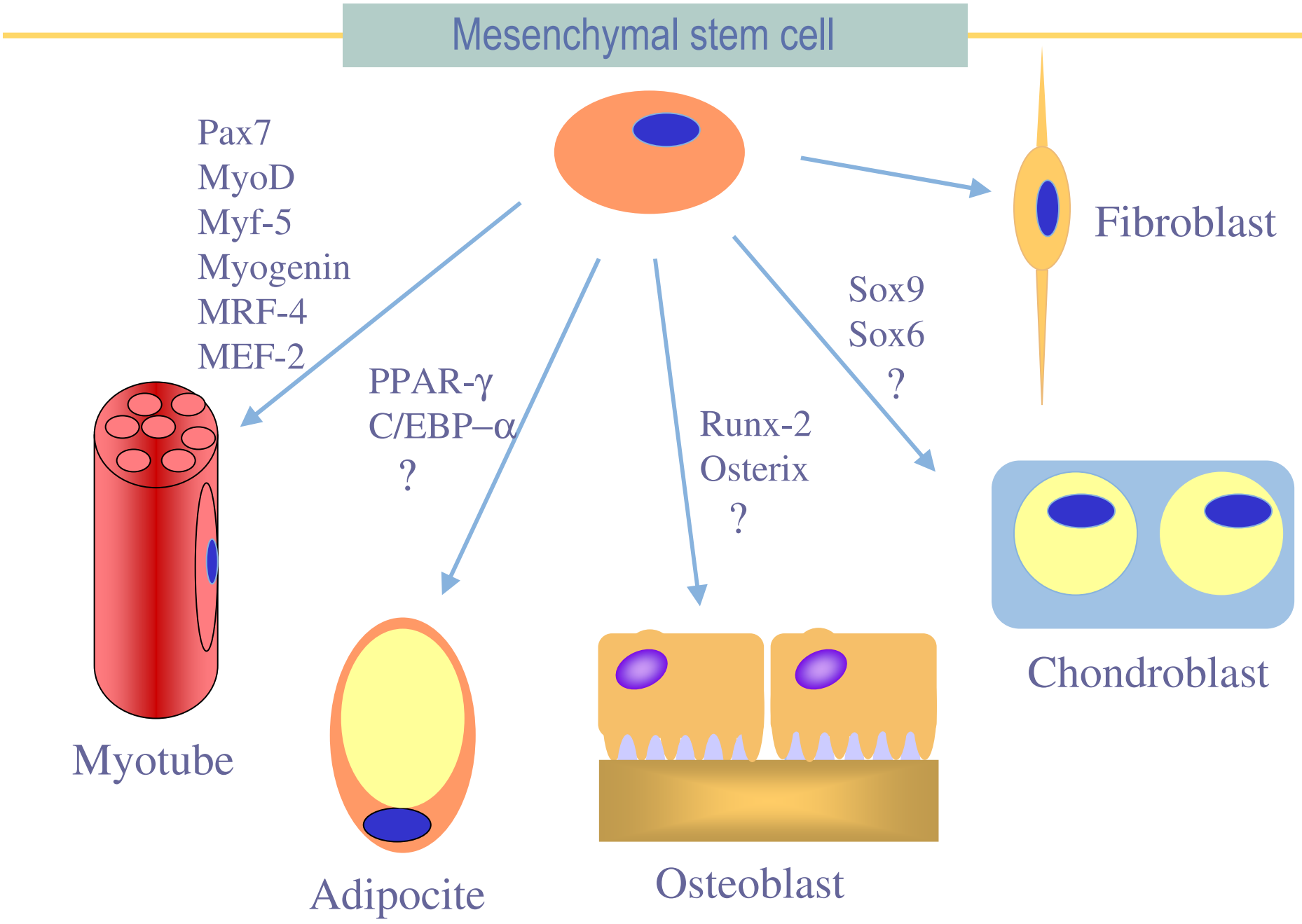
Knockouts of GDF-8 (myostatin)

Directed (mice)



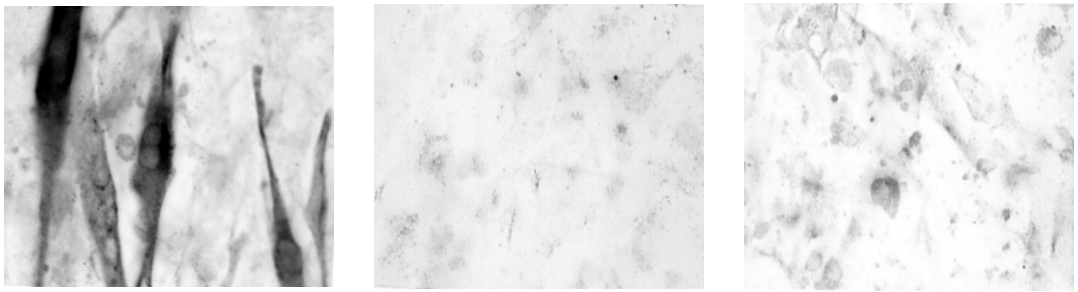
Selected (cow)

A.C. McPherron, A.M. Lawler, S.J. Lee. (1997) Nature 387:83–90.
Grobet L, Martin LJ, Poncelet D, et al. (1997) Nat Genet. 17:71-4.


Mesenchymal stem cell
Pax7
MyoD
Myf-5
Myogenin
MRF-4
MEF-2
PPAR-γ
C/EBP–α
?
Runx-2
Osterix
?
Sox9
Sox6
?
Fibroblast
Myotube
Adipocite
Osteoblast
Chondroblast

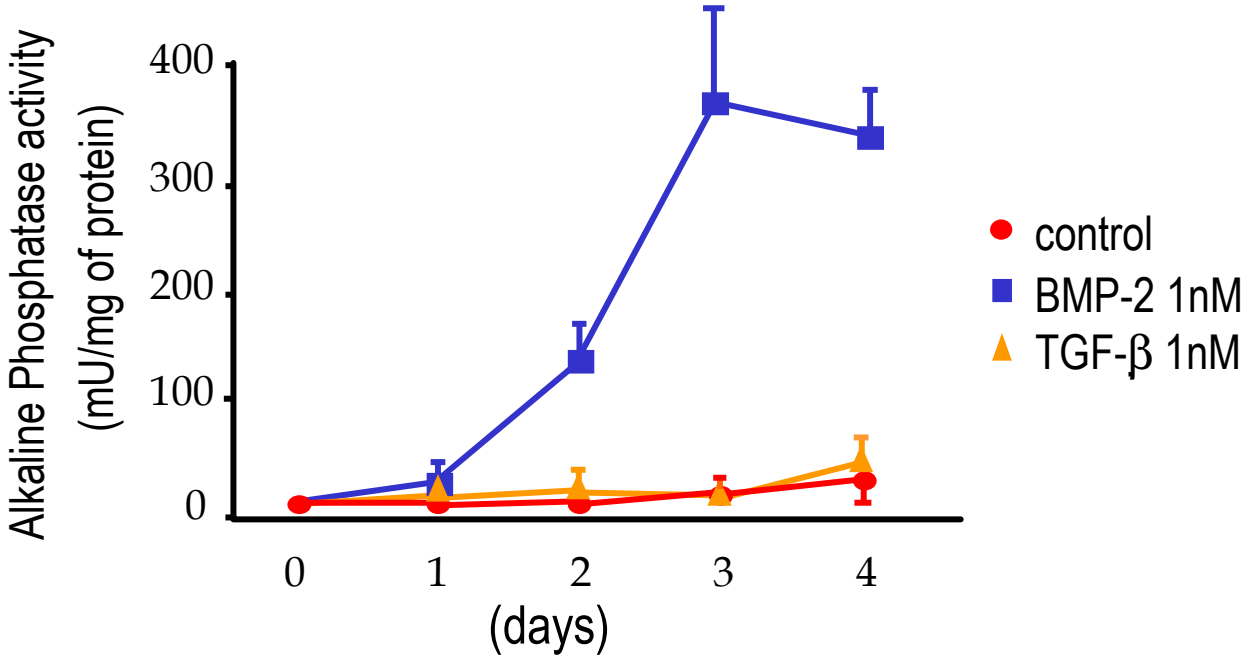
BMP-2 and TGF-β inhibit myoblast differentiation

Myogenic differentiation



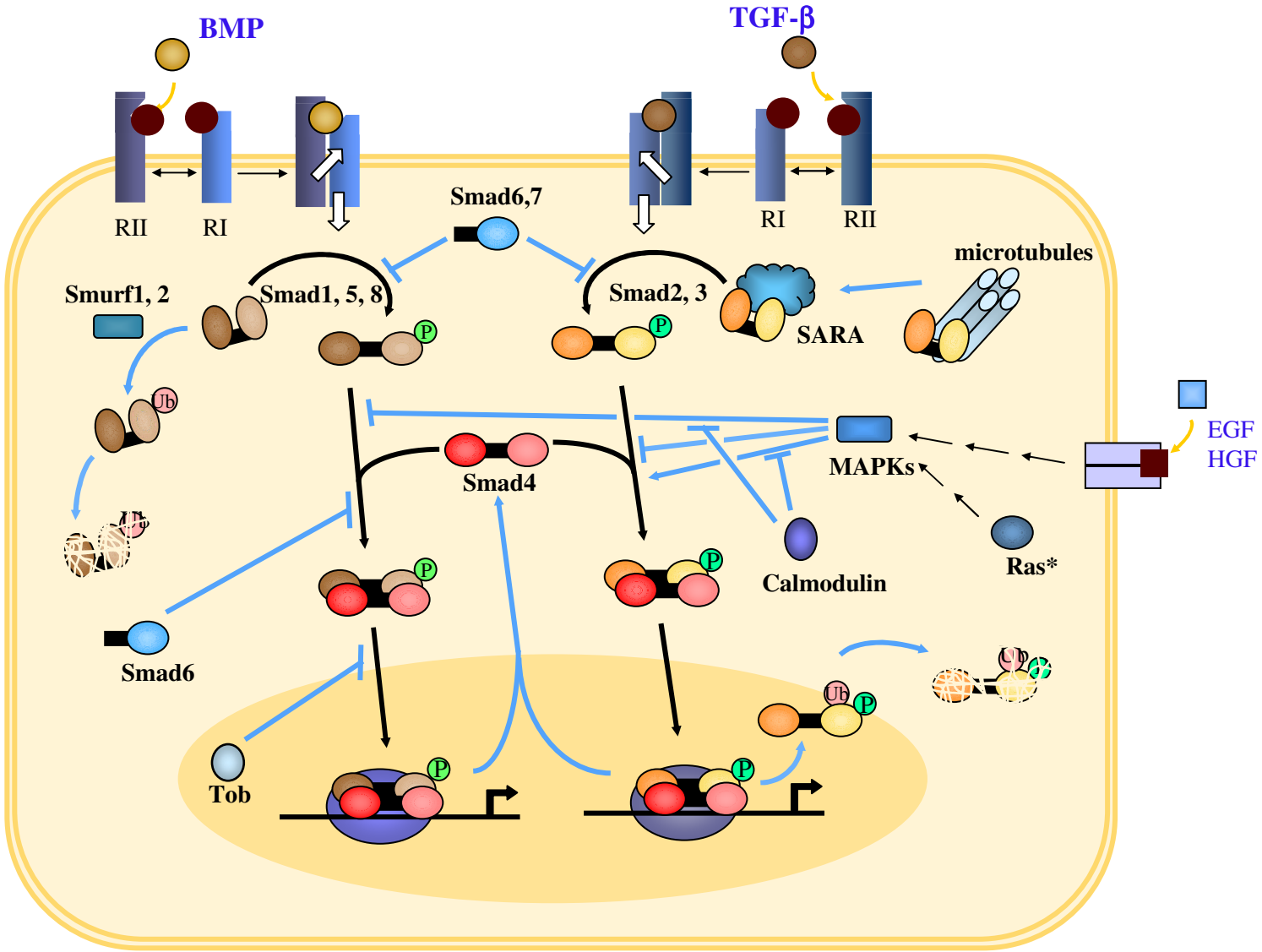
\- BMP-2 TGF-β

Osteoblast differentiation

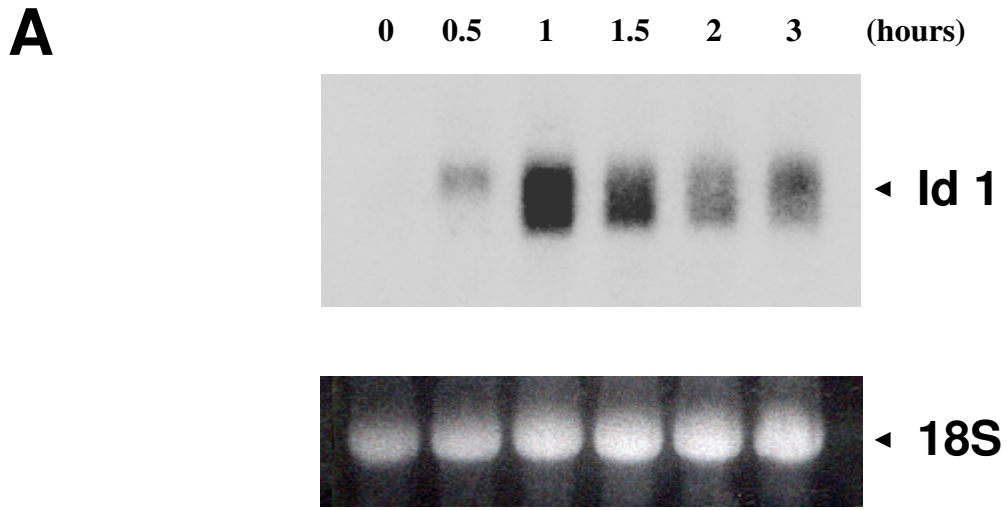


Chalaux E, López-Rovira T, Rosa JL, Bartrons R, Ventura F.
J Biol Chem. (1998) 273:537-43.

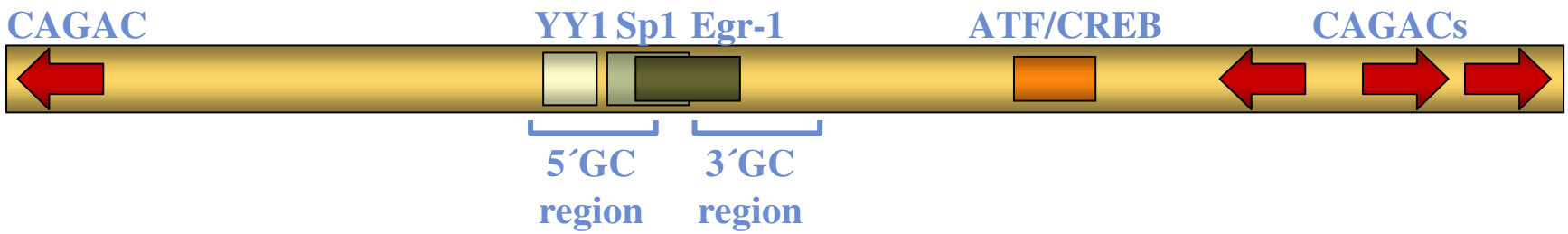
Smad signal transduction

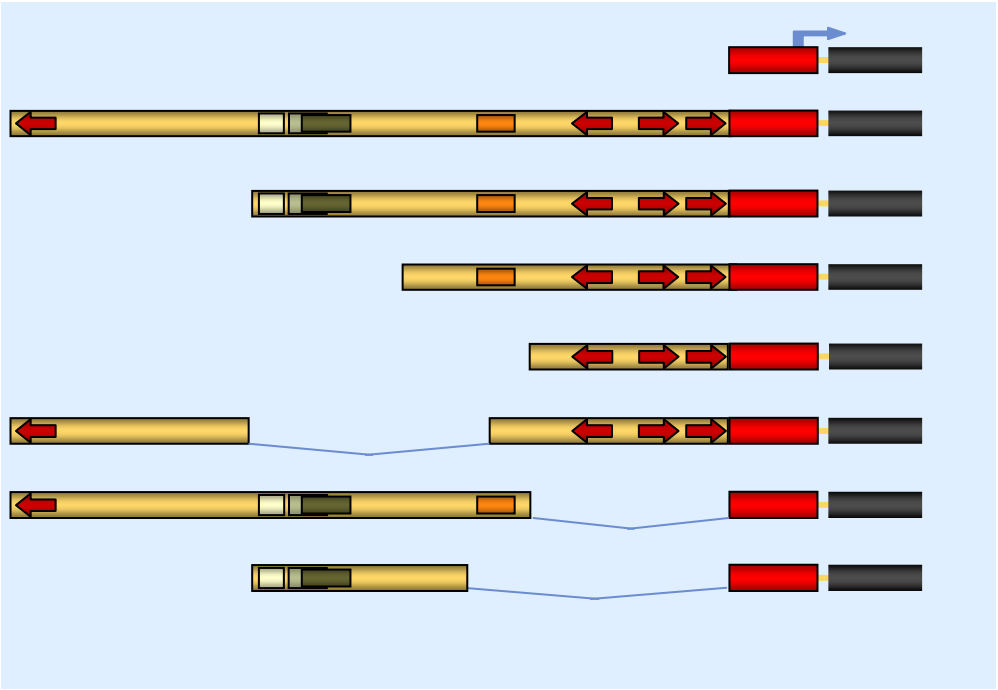


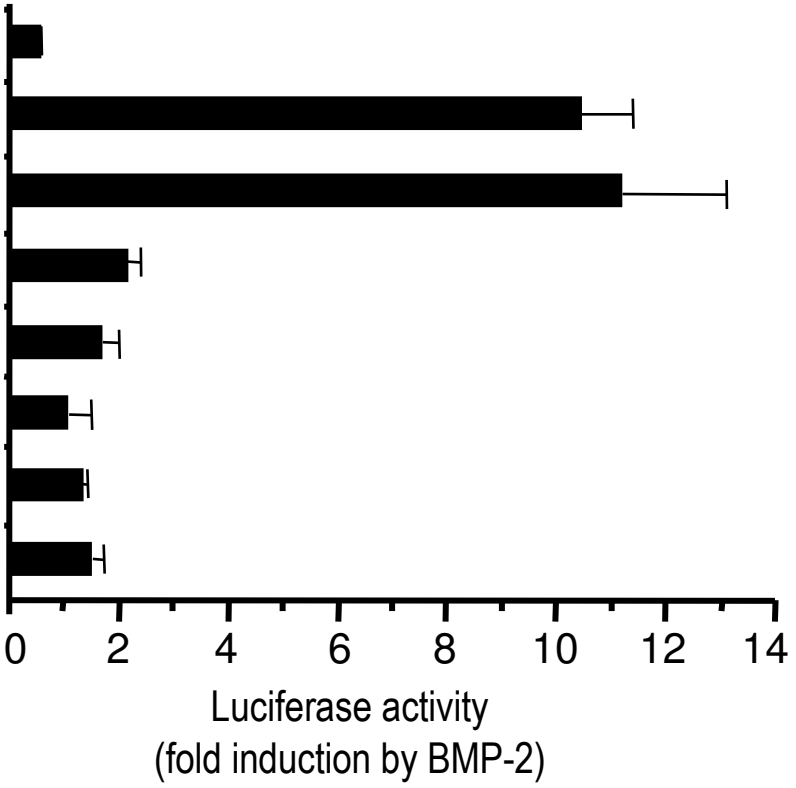
Id1 is an immediate response gene for BMP-2



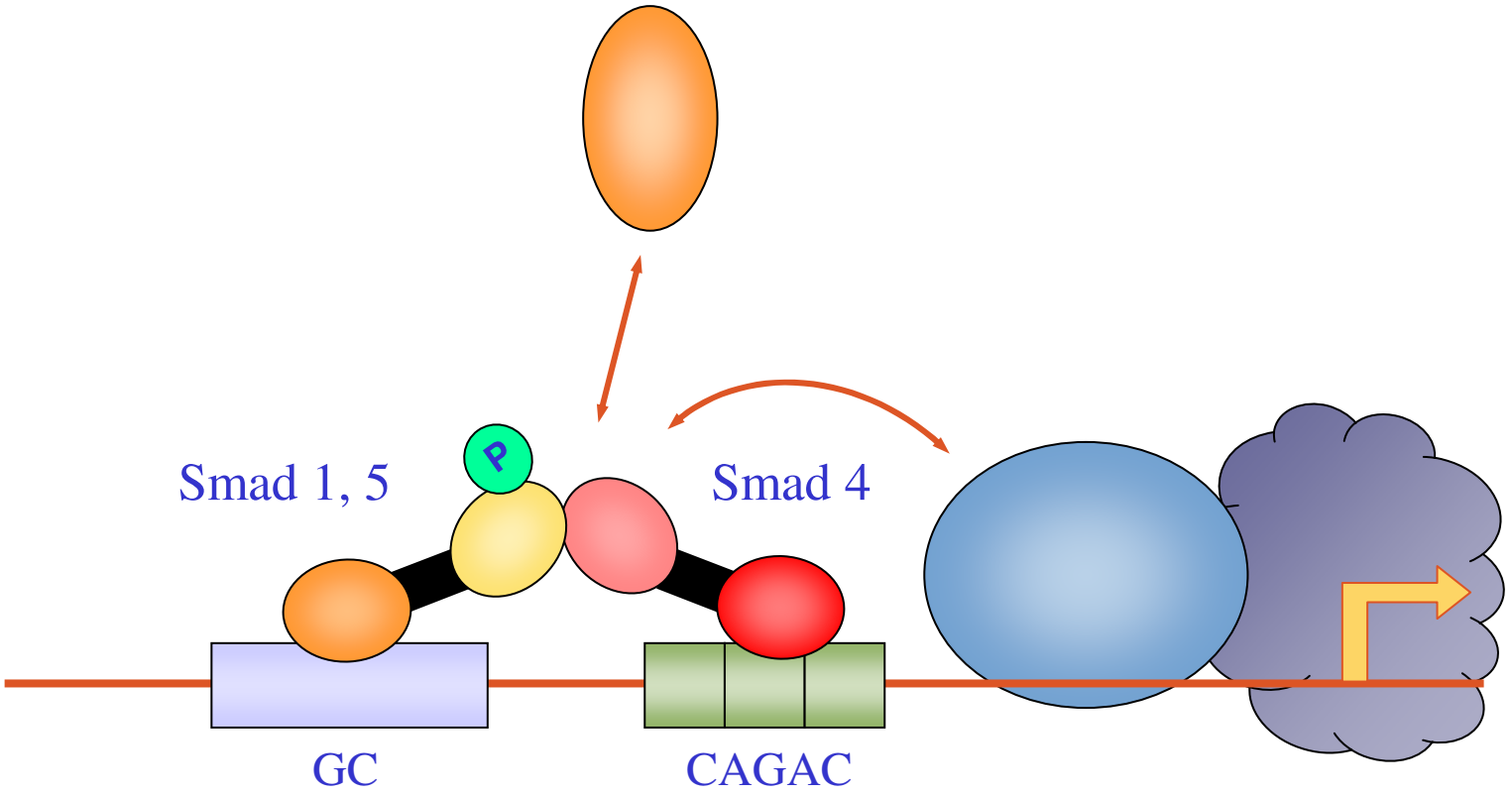
GC-rich and CAGAC elements are required for BMP-2 responses





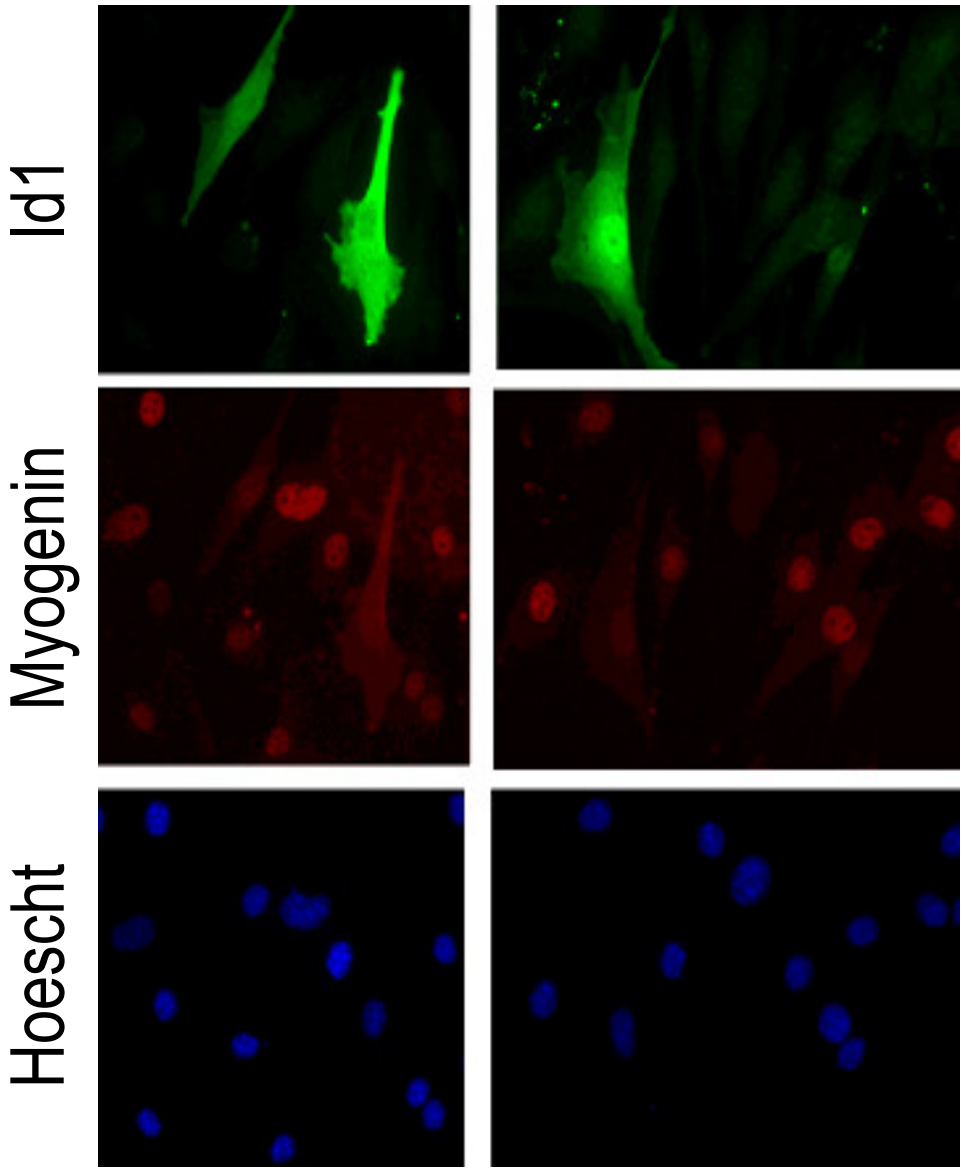


Smad binding model: the Id1 promoter

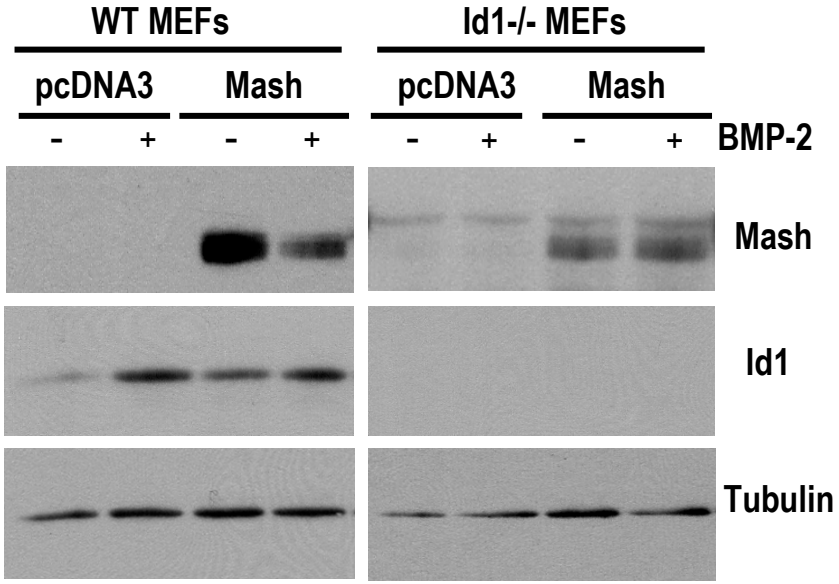


López-Rovira T, Chalaux E, Massagué J, Rosa JL, Ventura F.
J Biol Chem. (2002) 277:3176-85

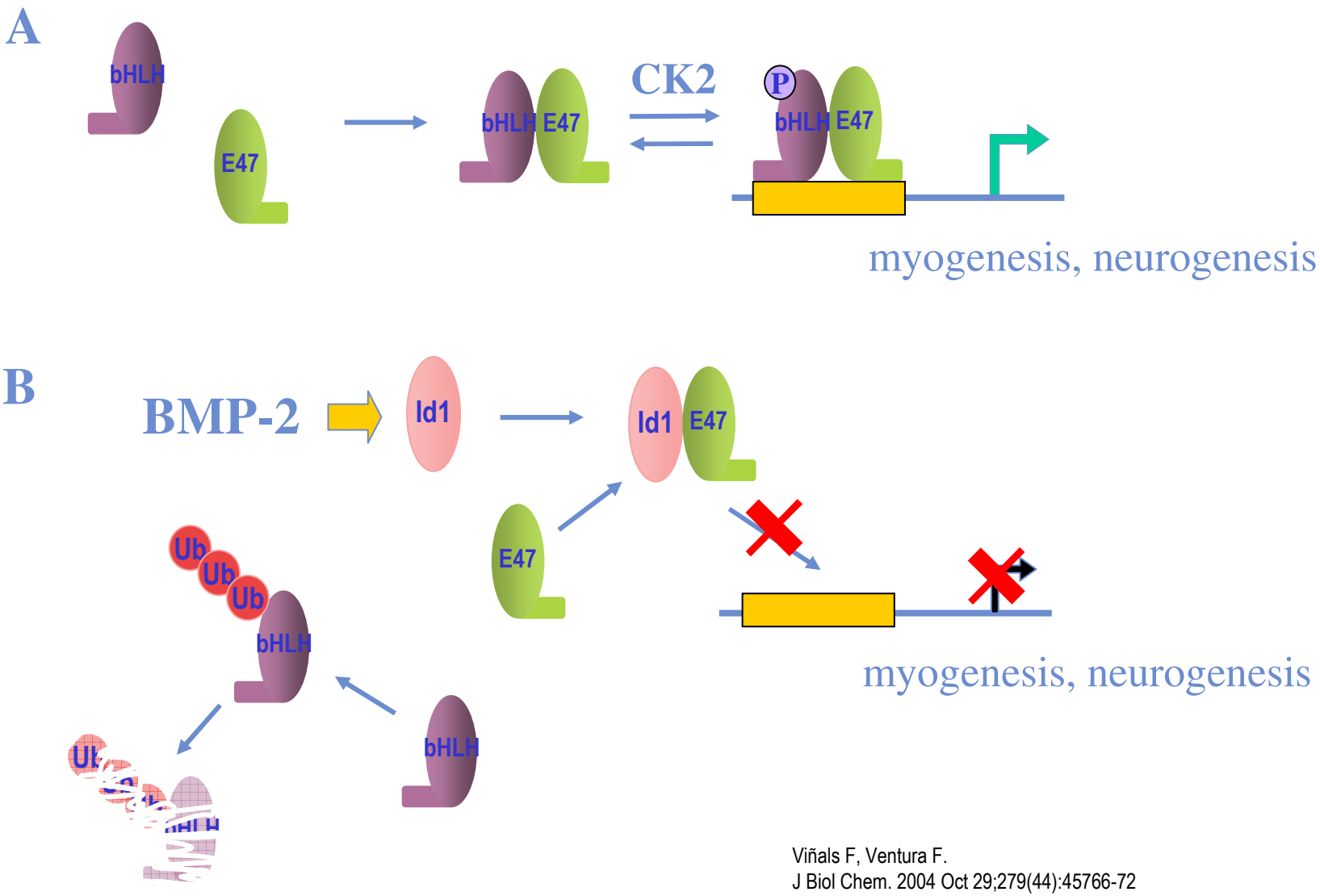
Id1 induction is sufficient for myogenin protein degradation



Id1 induction is necessary for bHLH protein degradation

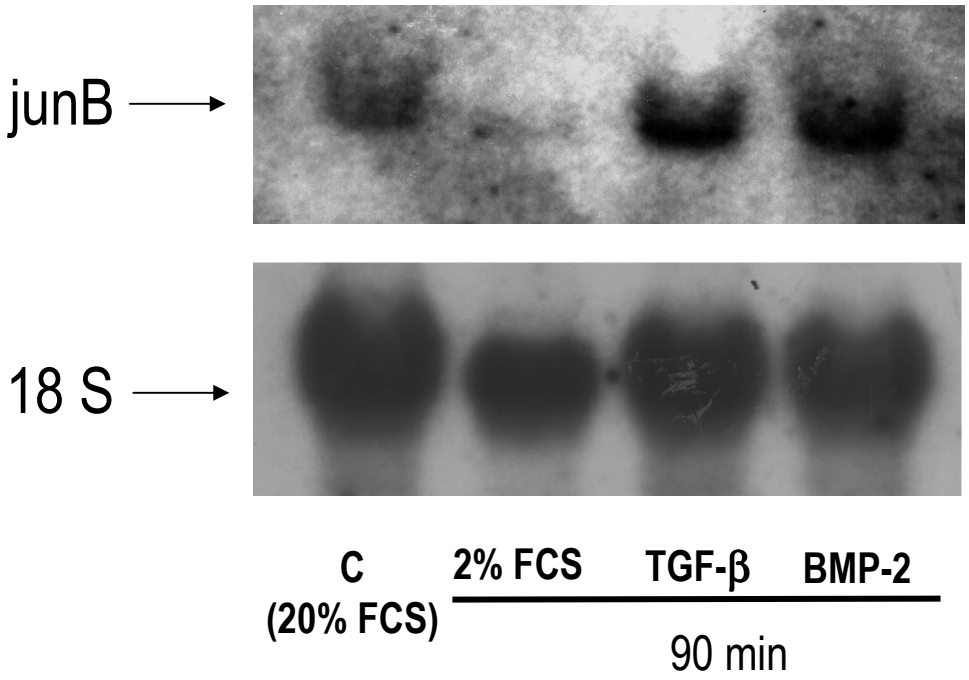


Regulatory mechanisms of repression of bHLH by BMP-2/Id1

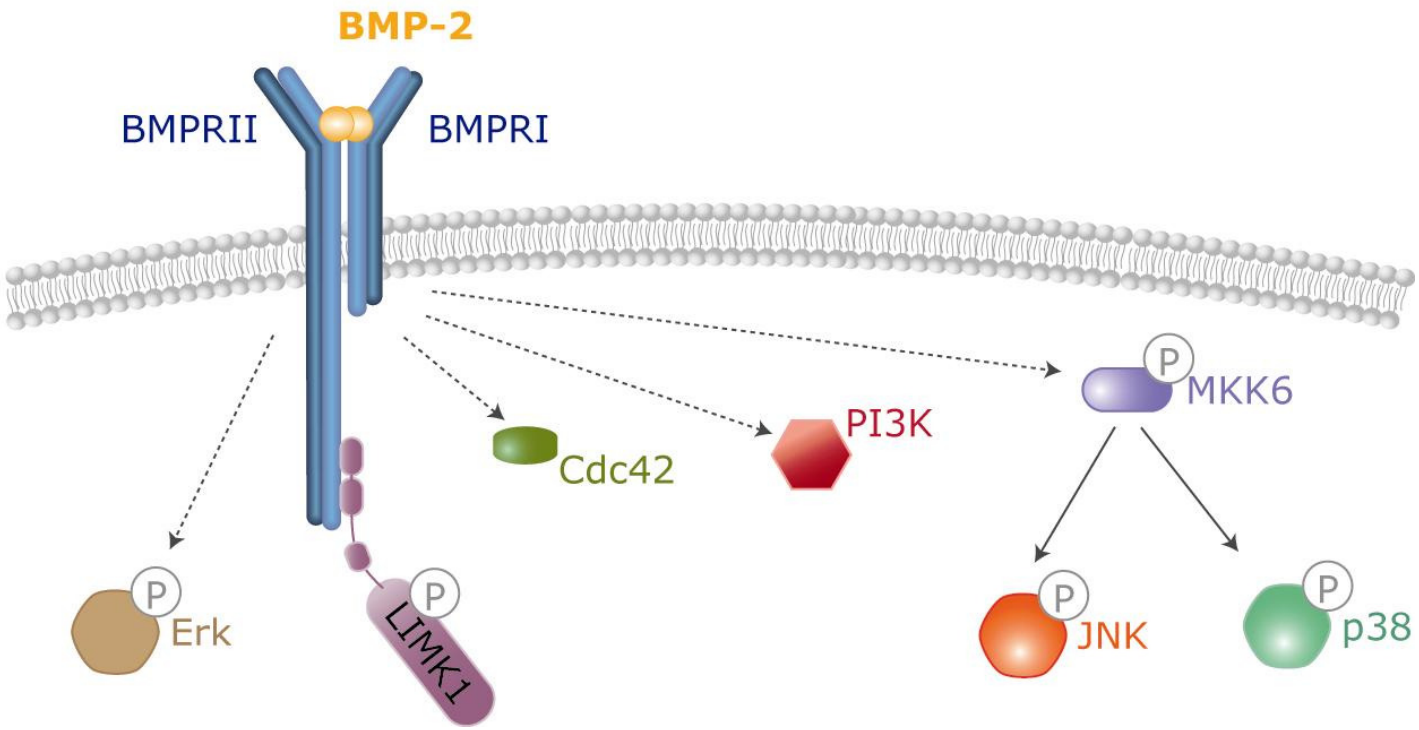


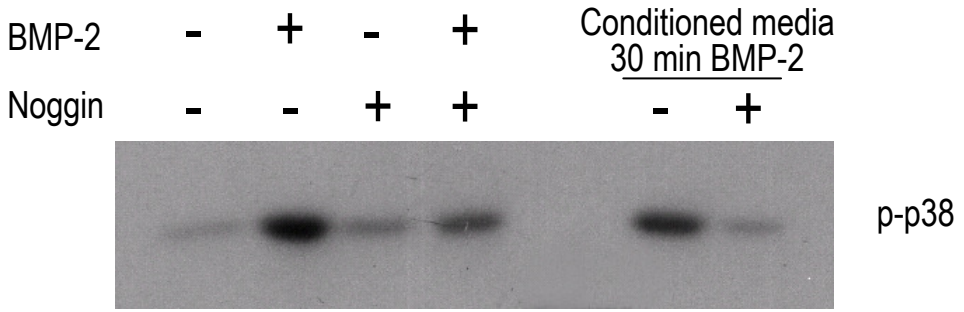
Viñals F, Ventura F.
J Biol Chem. 2004 Oct 29;279(44):45766-72
Viñals F, Reiriz J, Ambrosio S, Bartrons R, Rosa JL, Ventura F.
EMBO J. 2004 Sep 1;23(17):3527-37

JunB is induced by TGF-β and BMP-2 in Smad 4 deficient cells (NP29)

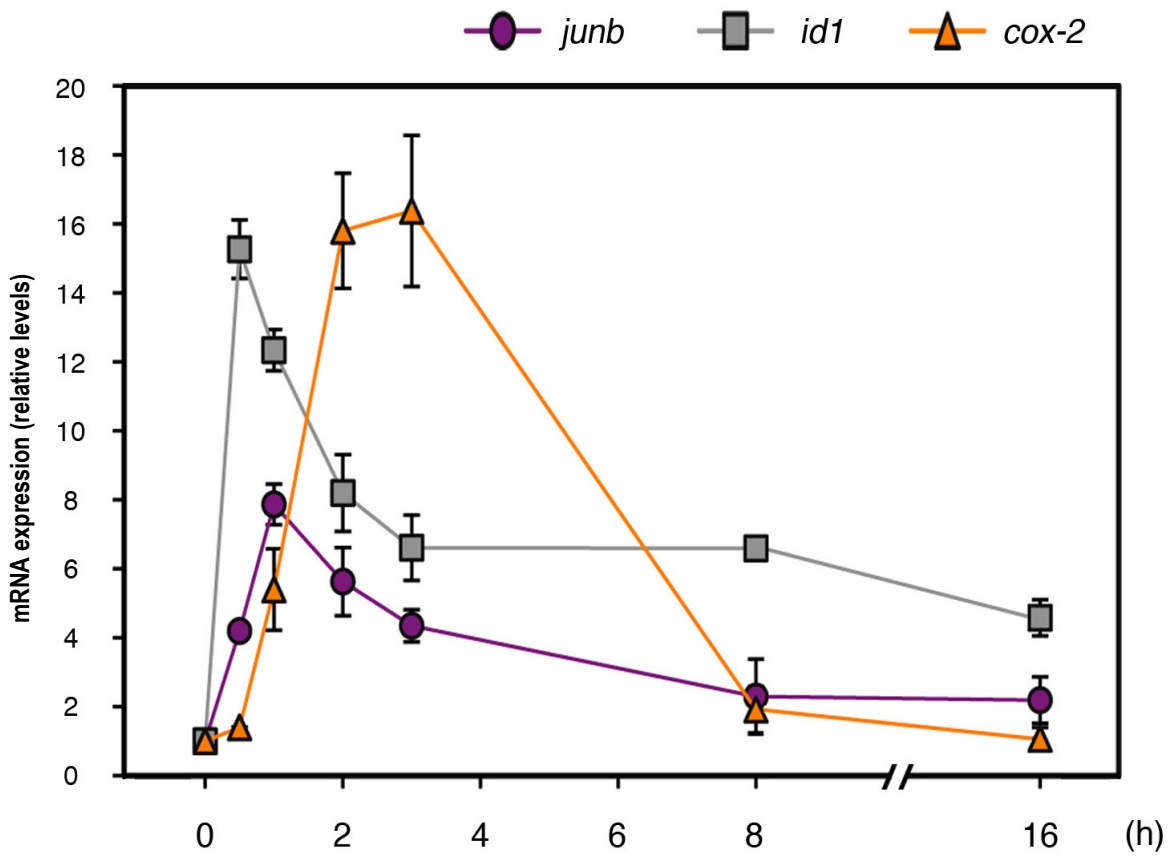


Non-canonical BMP signal transduction

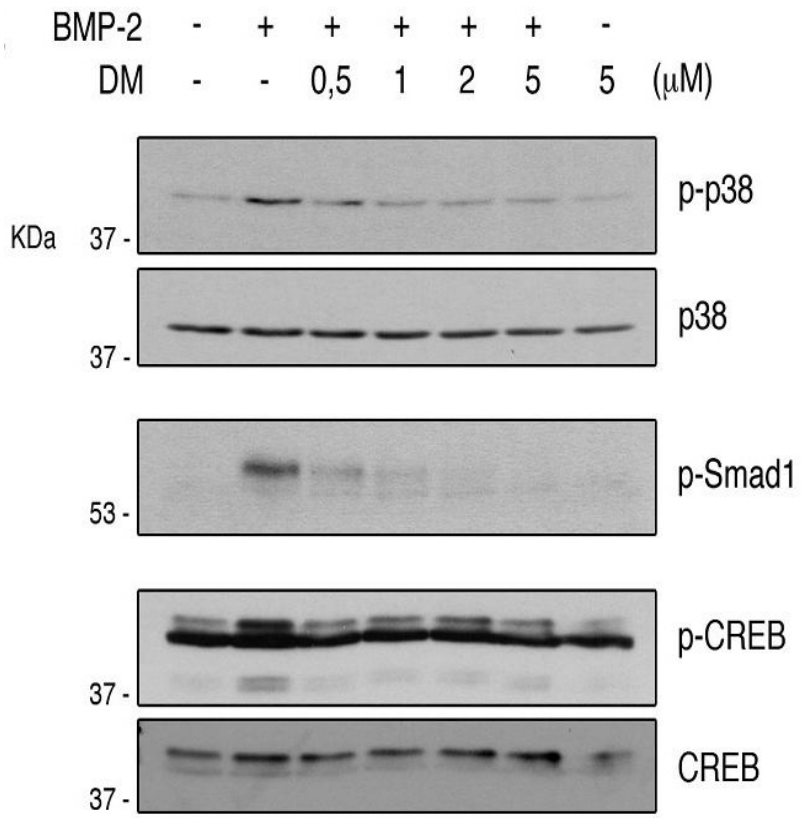


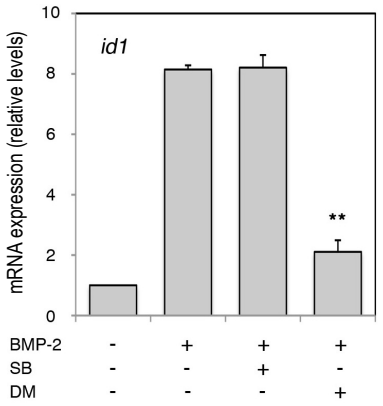


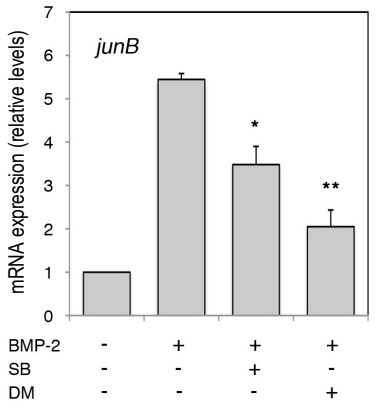
Distinct immediate early genes differ in their kinetics of BMP-2 induction

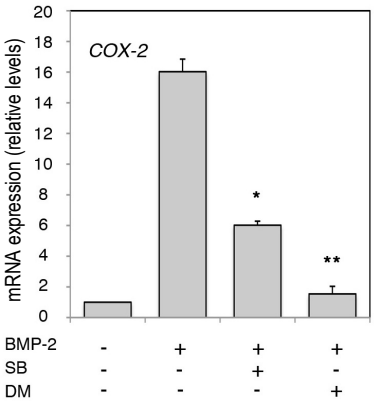


Transcriptional induction of JunB and Cox2 by BMP-2 depends on p38

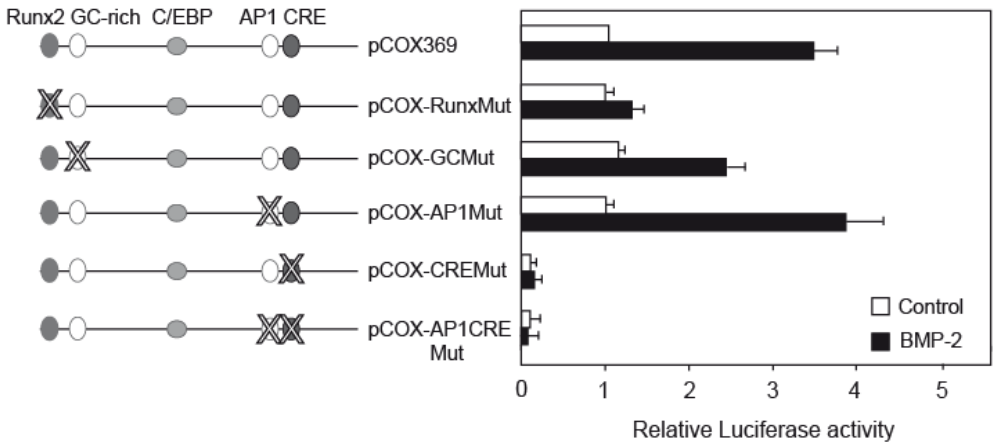


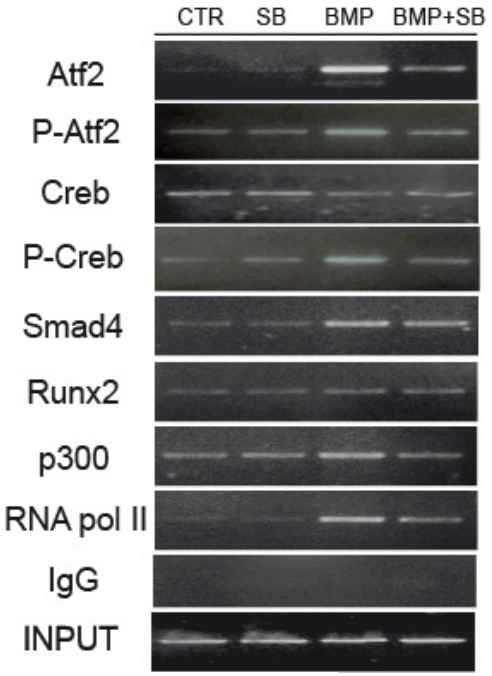


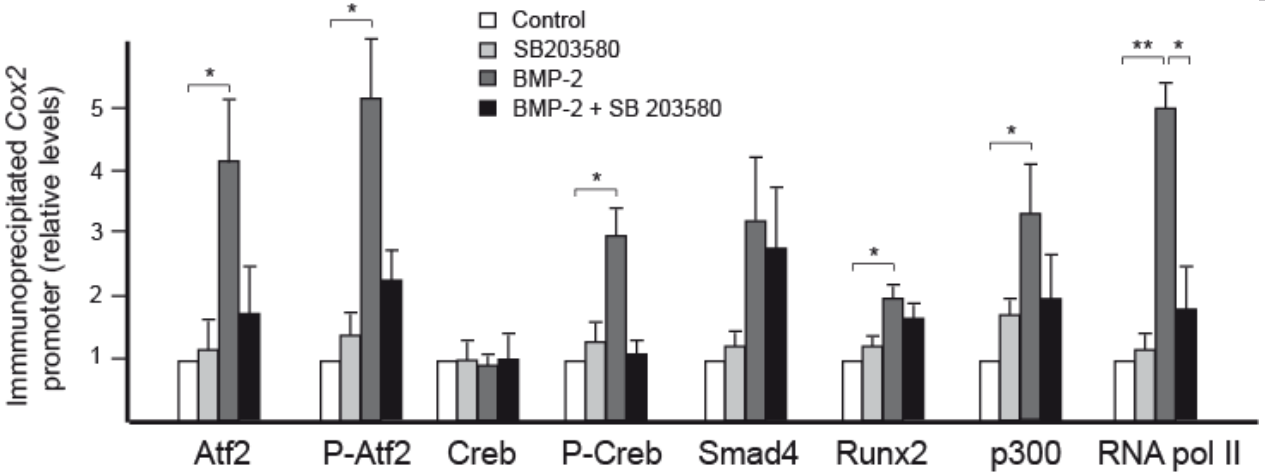


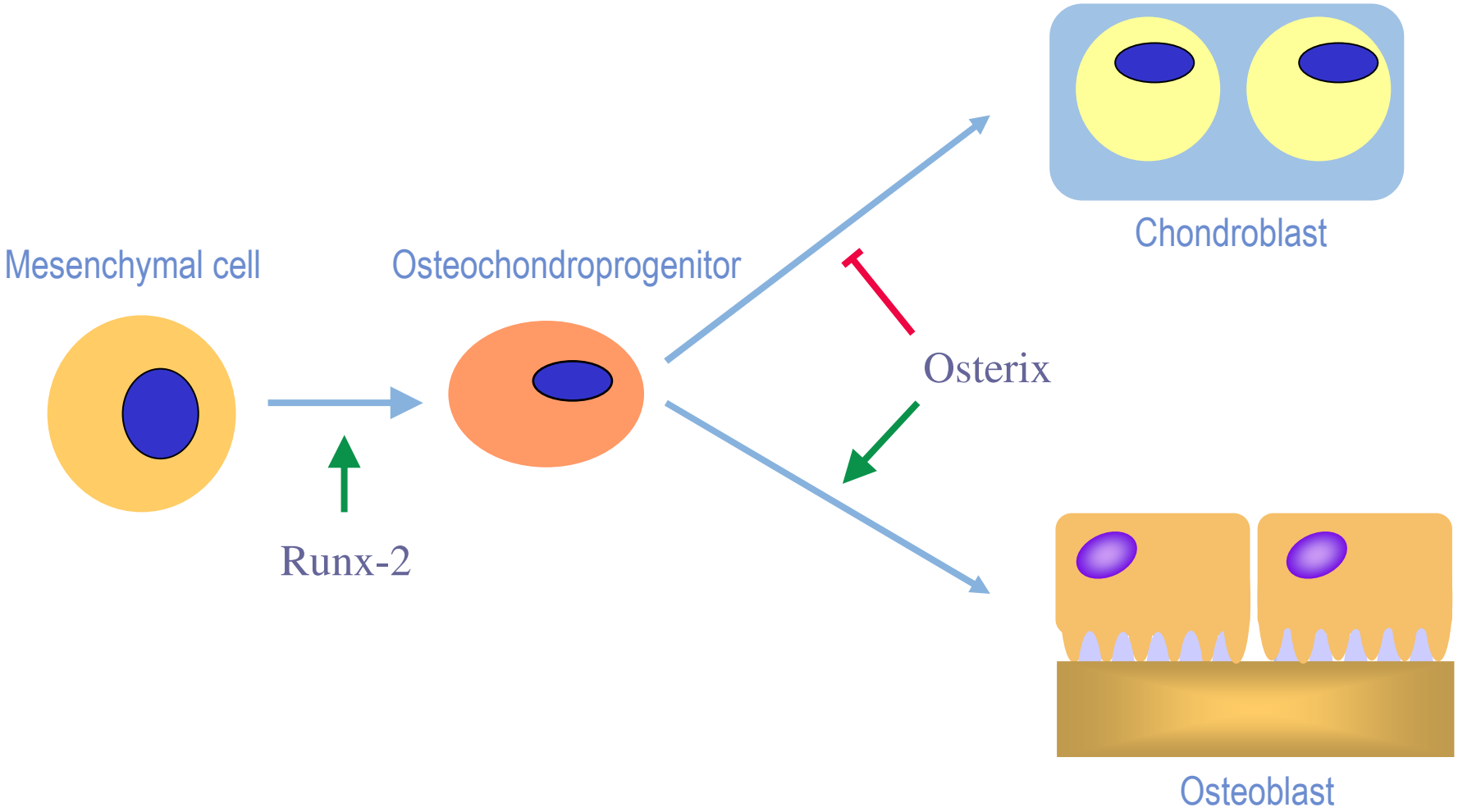


GC-rich, Runx2 and CRE elements are required for BMP-2 responses



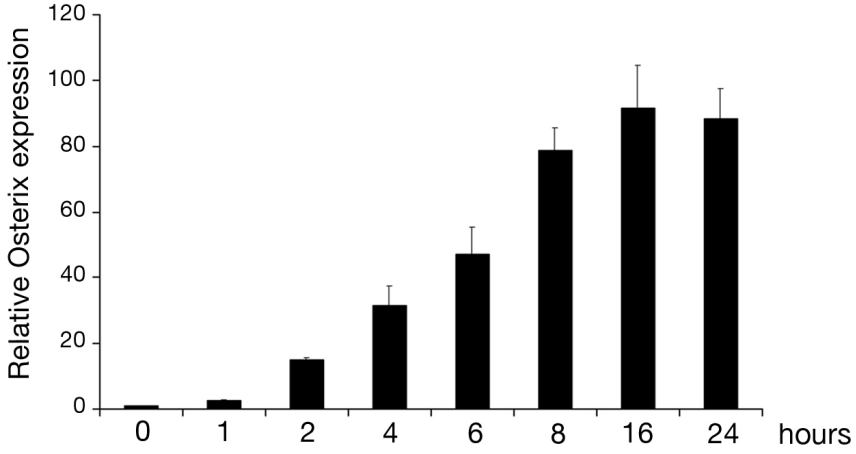




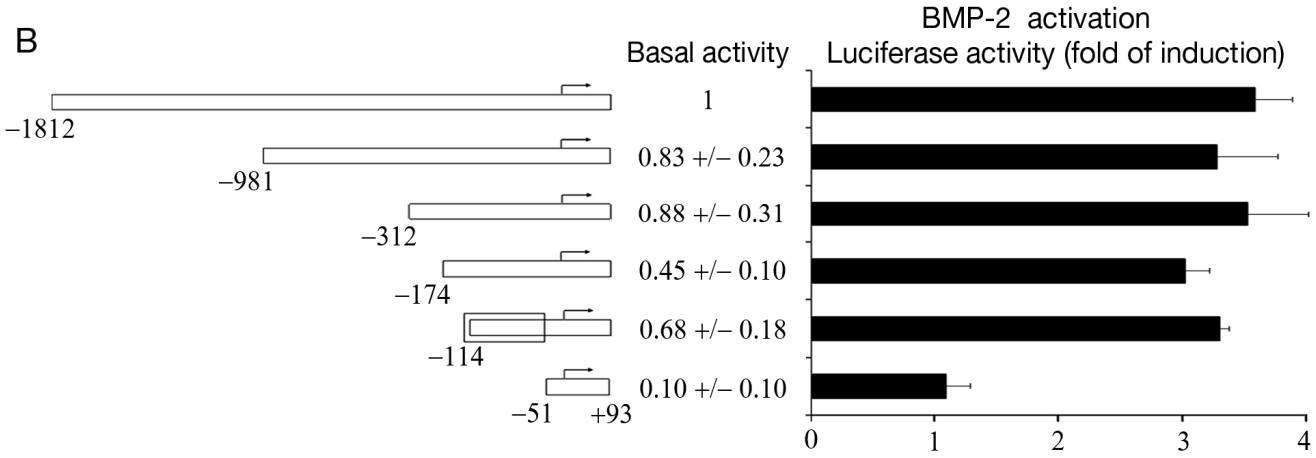

Mesenchymal cell
Osteochondroprogenitor
Runx-2
Osterix
Chondroblast
Osteoblast

BMP-2 induces Osterix expression

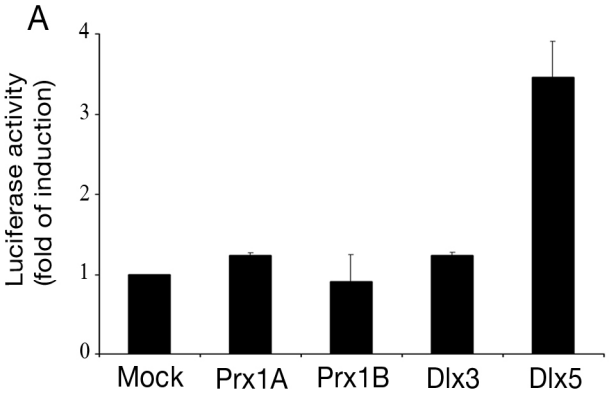
A

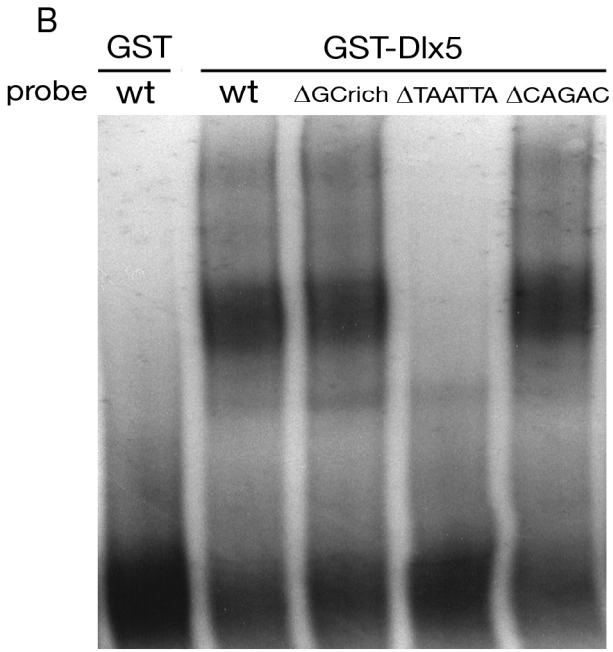


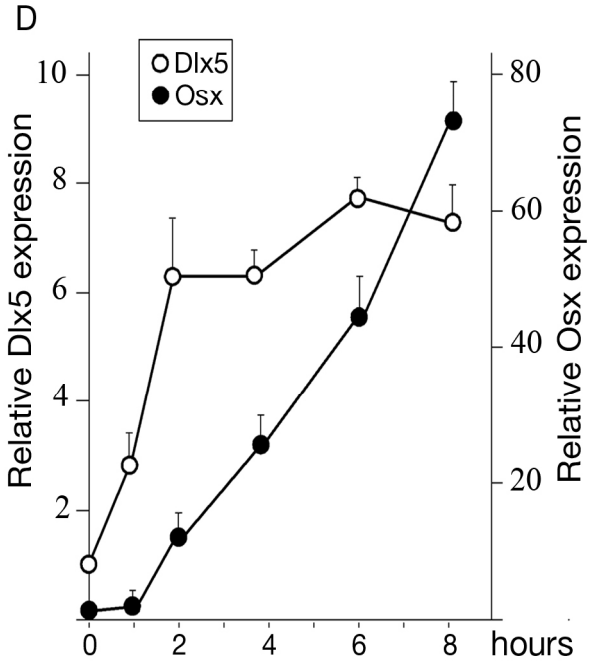
B



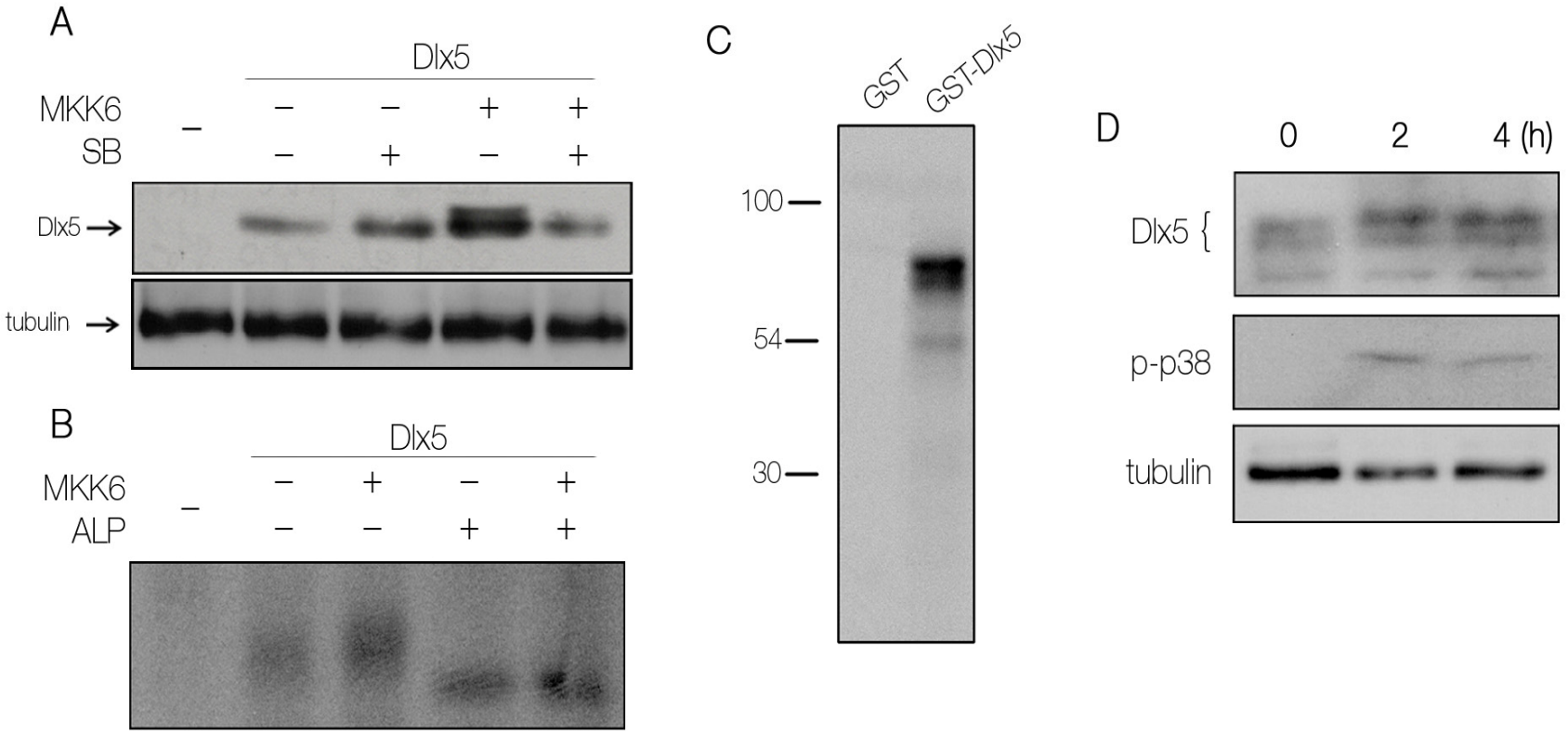
Dlx5 binds and activates Osx promoter



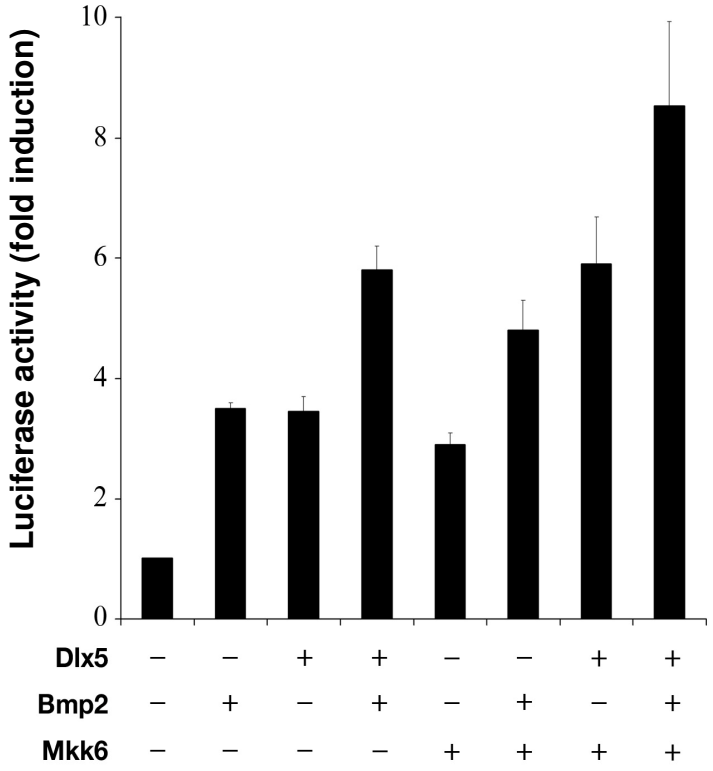


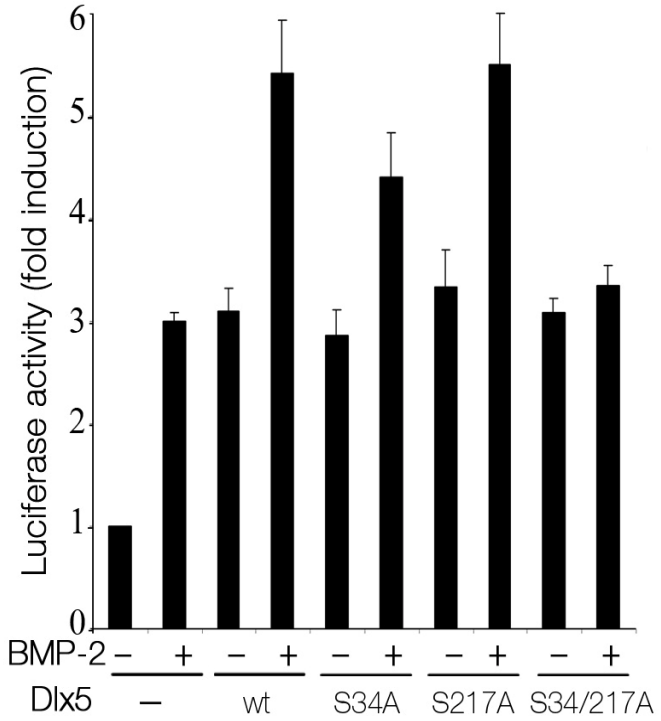


p38 phosphorylates Dlx5

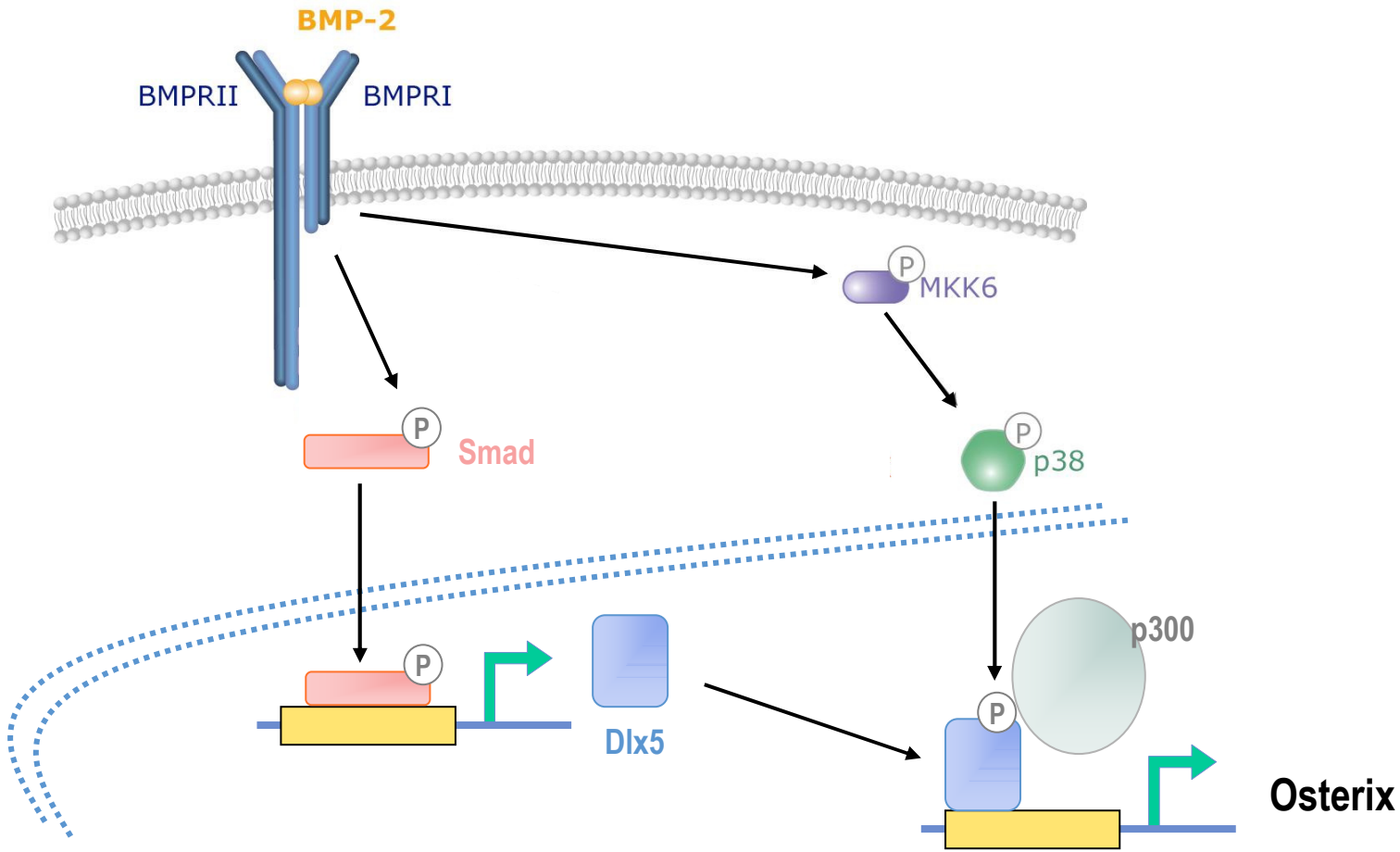


p38 phosphorylation enhances Dlx5 transcriptional activity



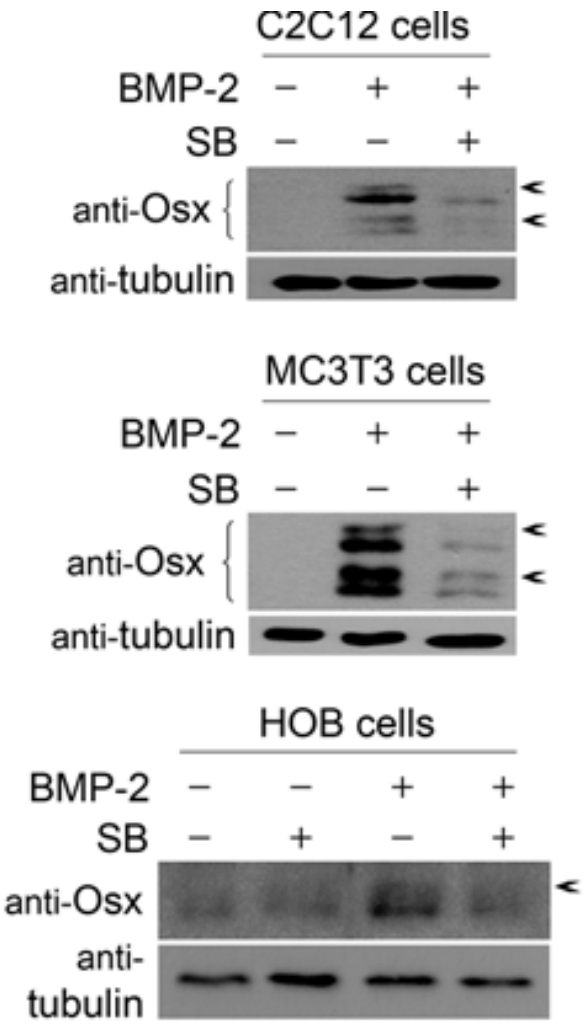


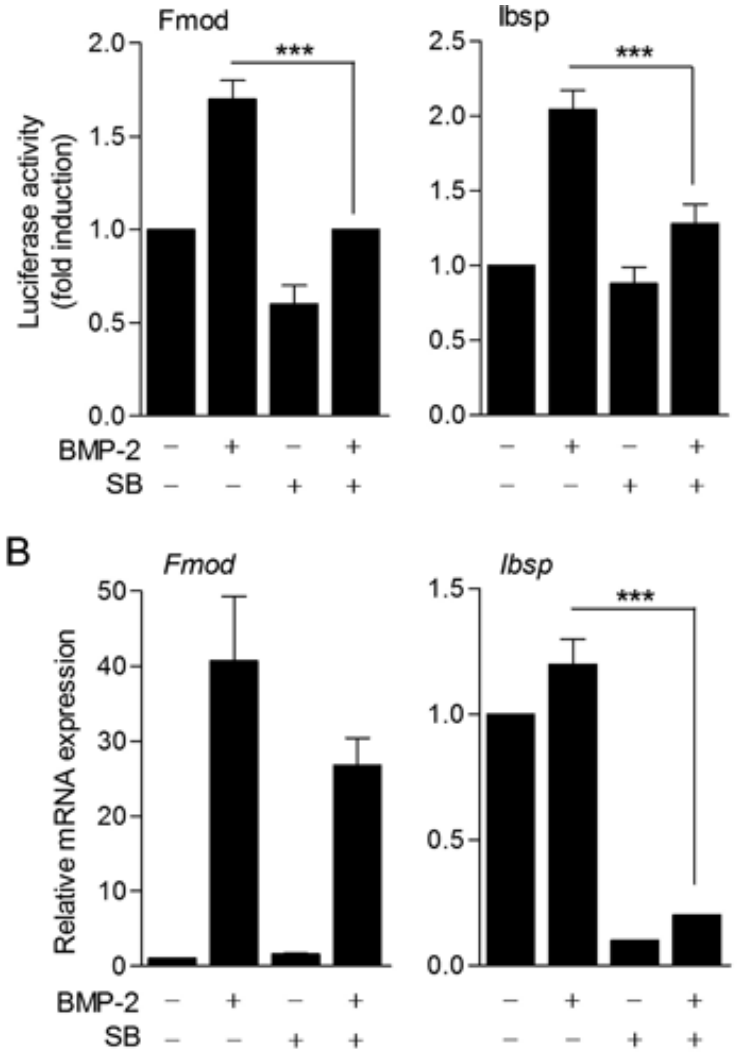
Dlx5 integrate Smad-dependent and independent signal transduction



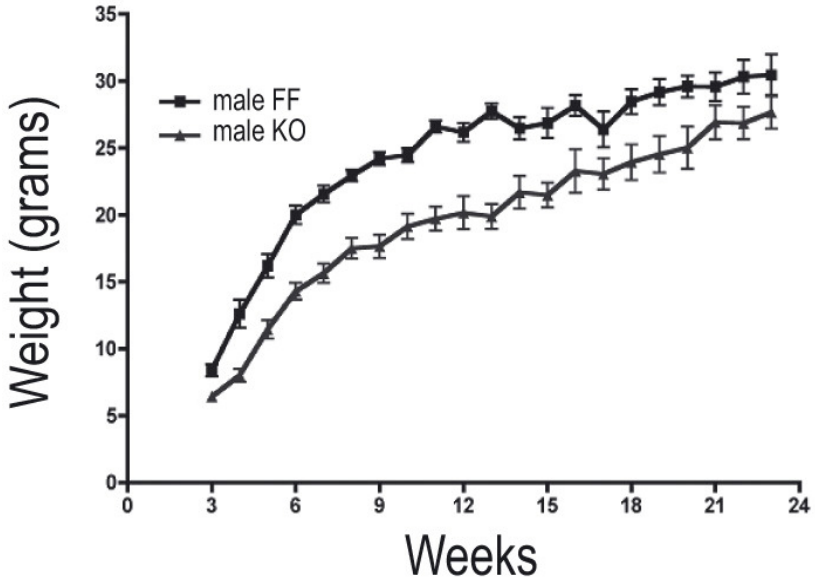
Ulsamer, A., Ortuño, M.J., Ruiz, S., Susperregui, A.G., Osses, N., Rosa, J.L:, Ventura F.
J Biol Chem. (2008) 283:3816-26.

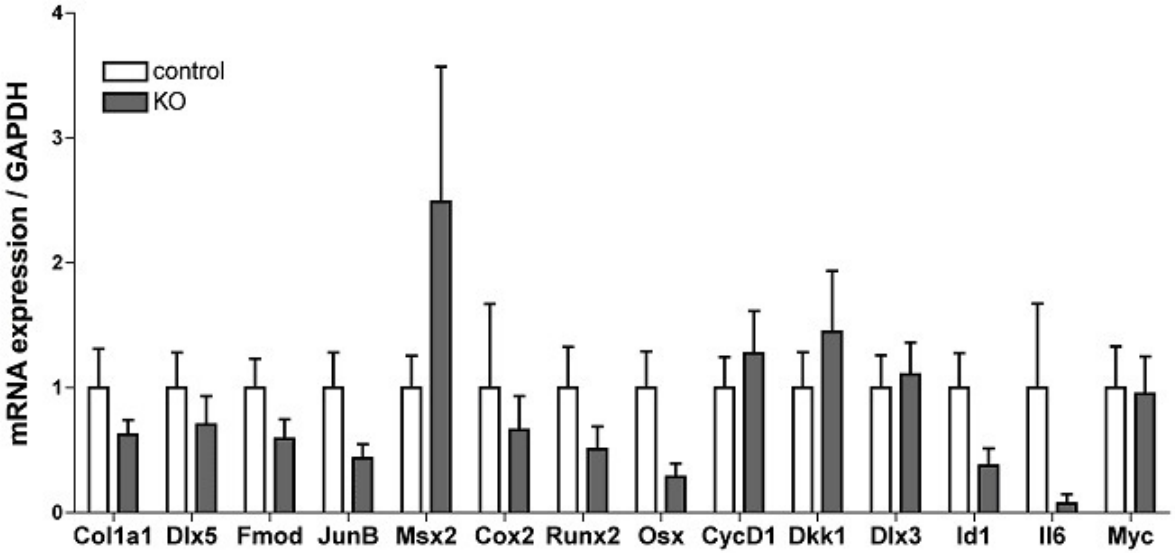
p38 phosphorylation enhances Osx transcriptional activity



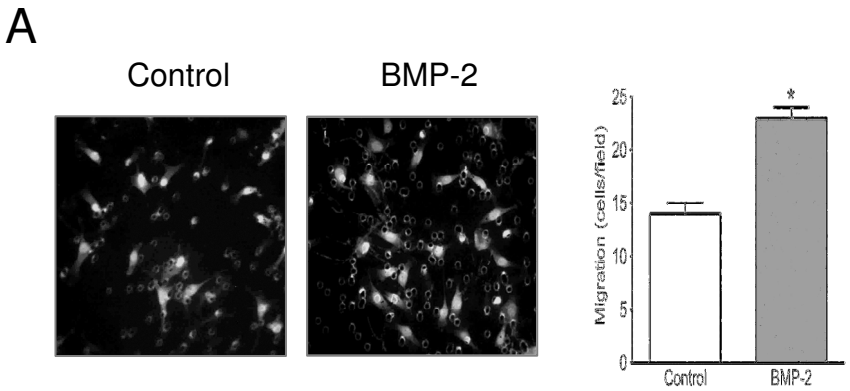


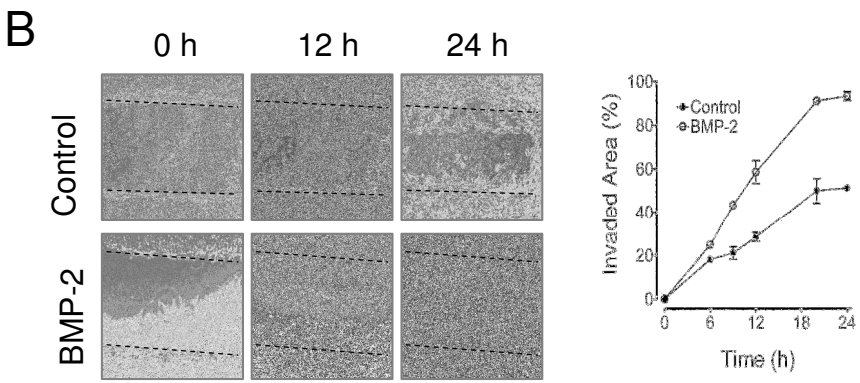
Osteoblast-specific p38α deficient mice display impaired osteogenesis

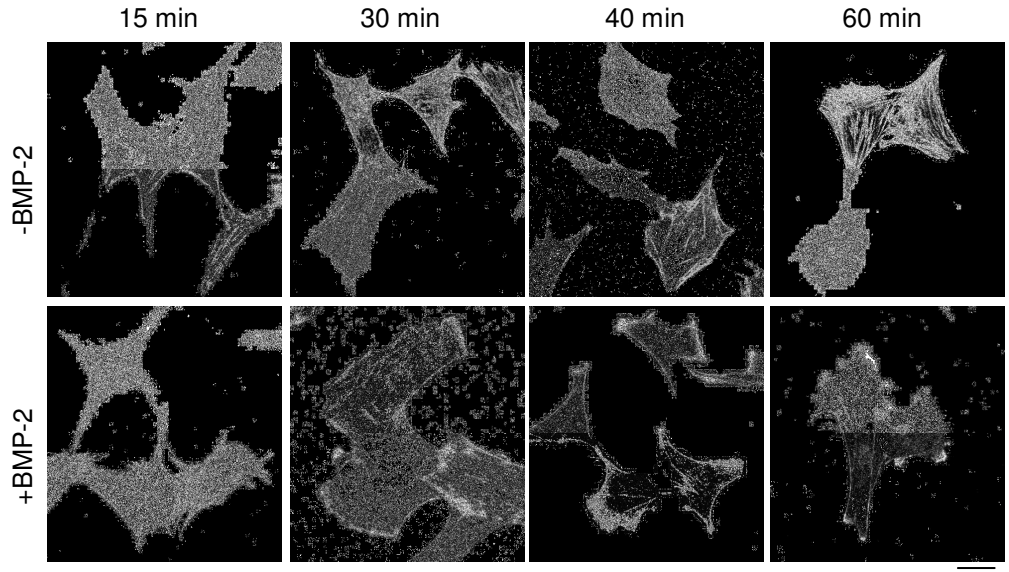


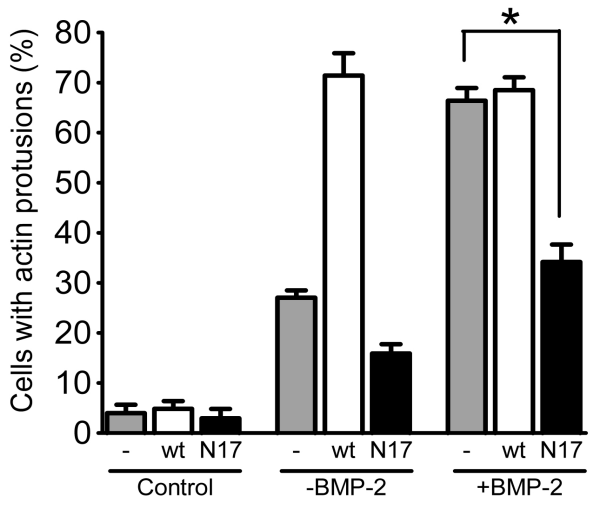


BMP-2 induces cell migration through Cdc42

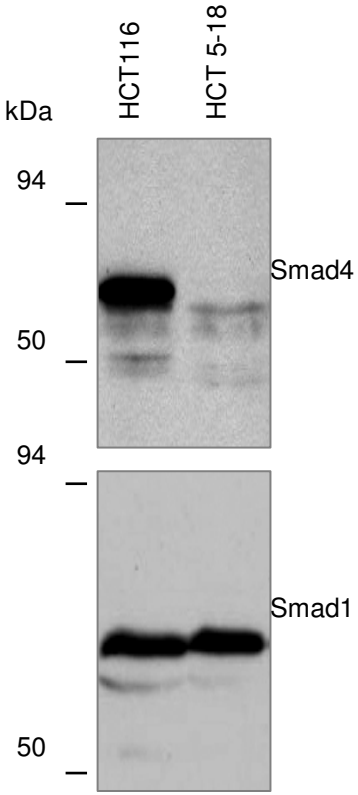


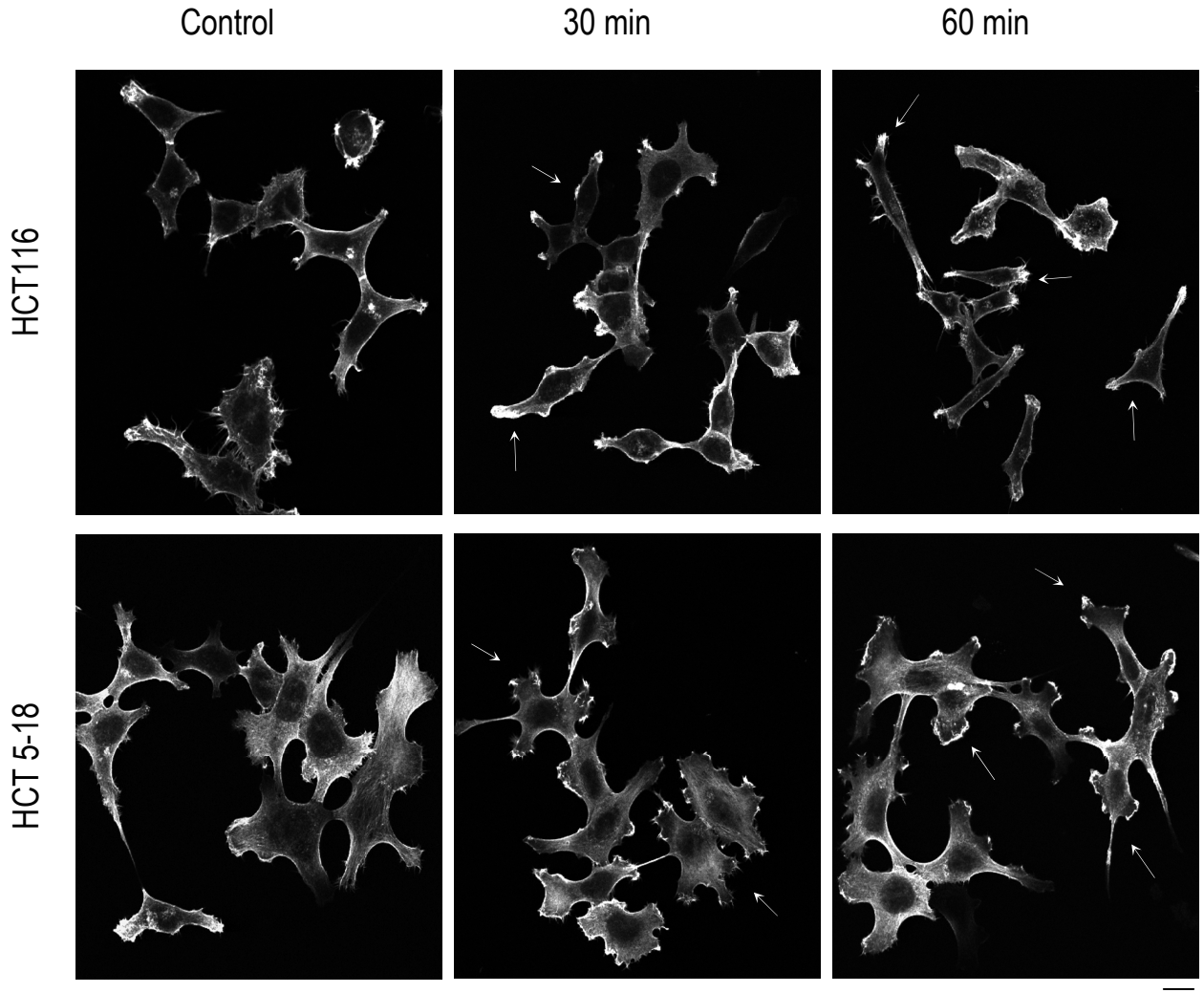




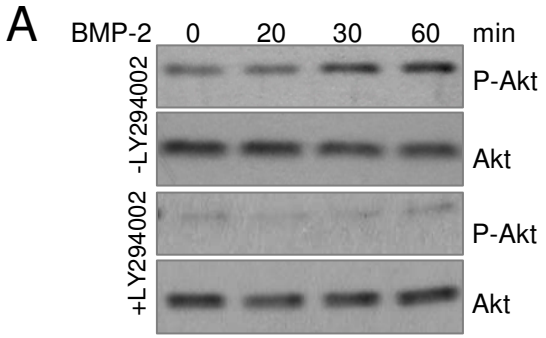


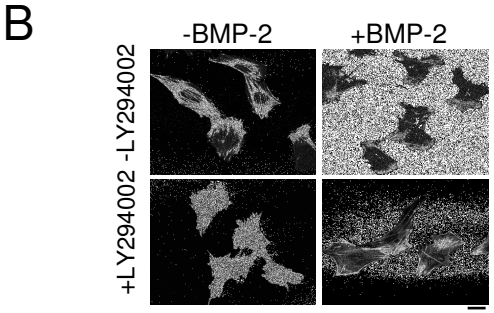
BMP-2 effects on cytoskeletal reorganization are Smad-independent

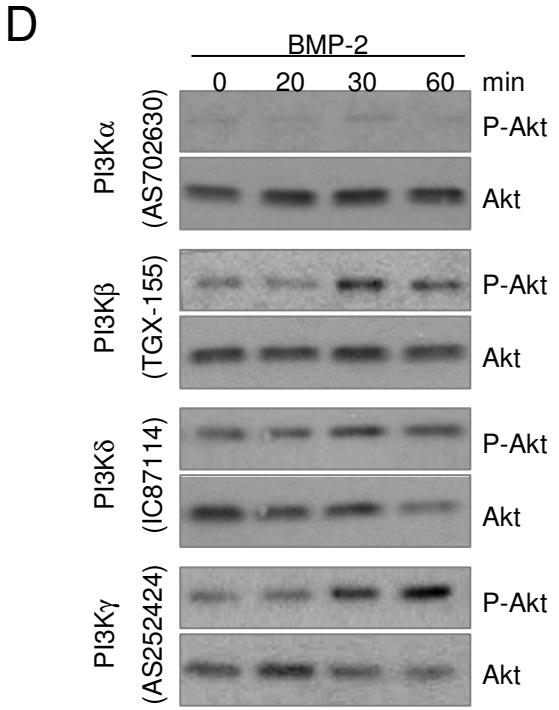


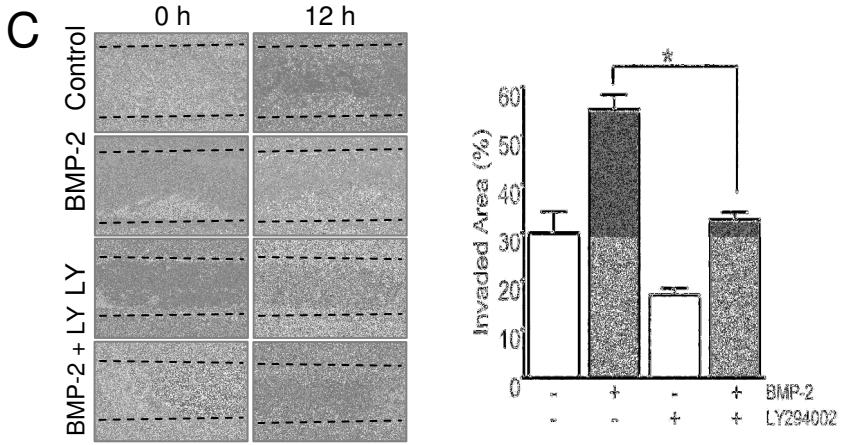


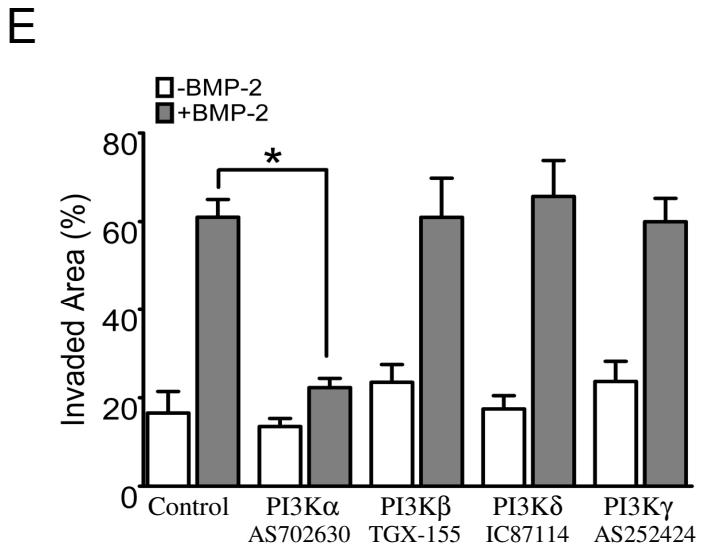
PI3K activity is required for BMP-2 induced cell migration



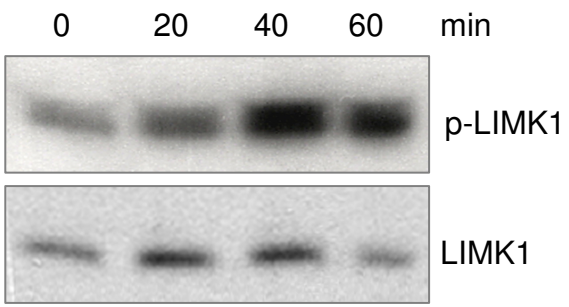


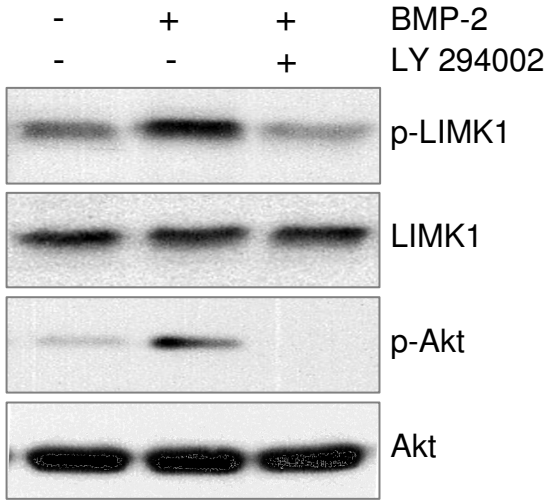


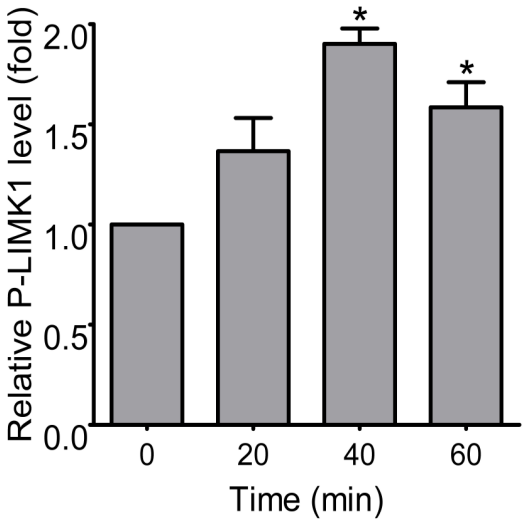


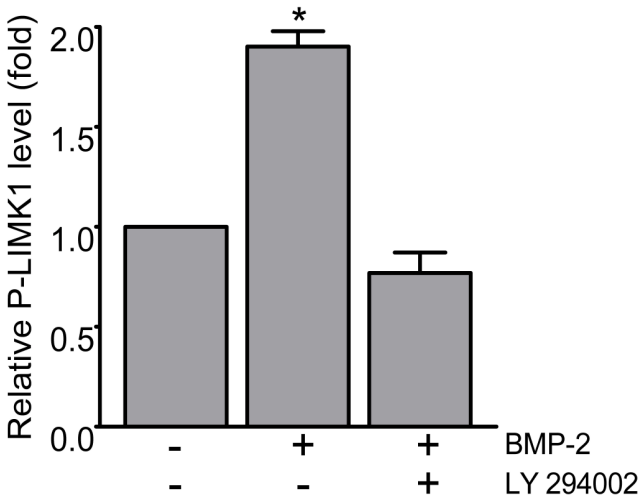


PI3K activity is required for BMP-2 induced LIMK activity

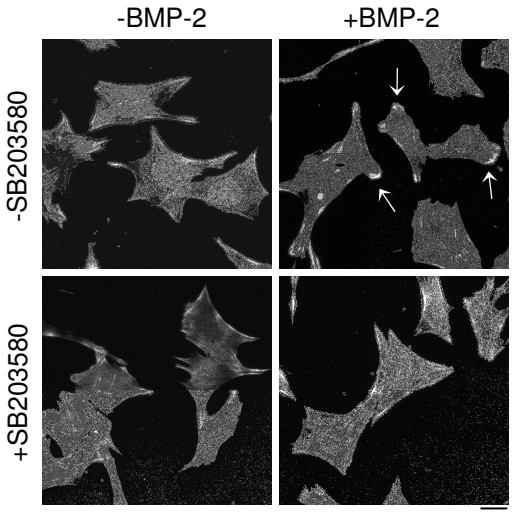


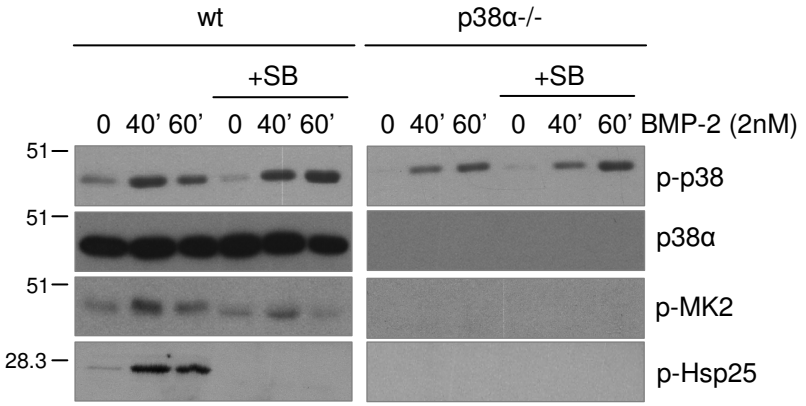


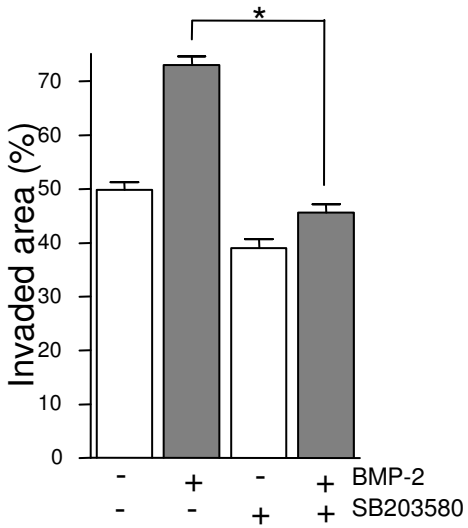


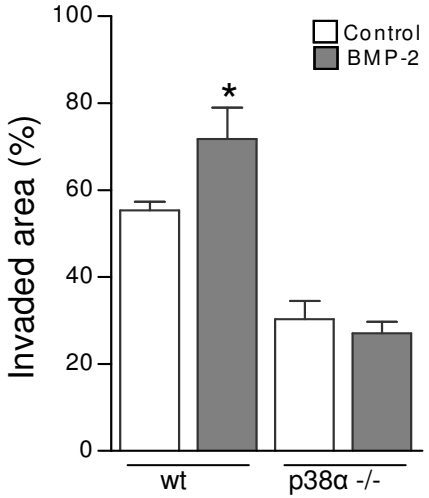


p38 is also required for BMP-2 induced migration

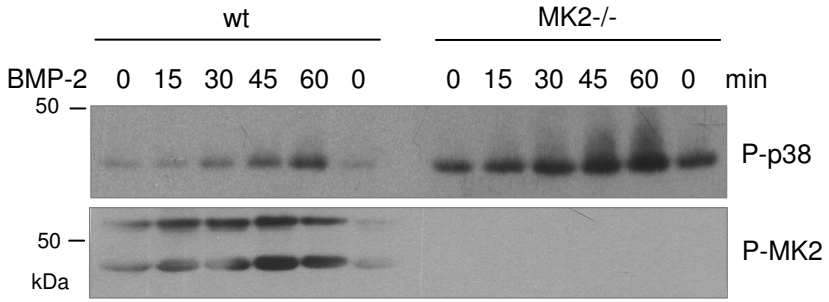


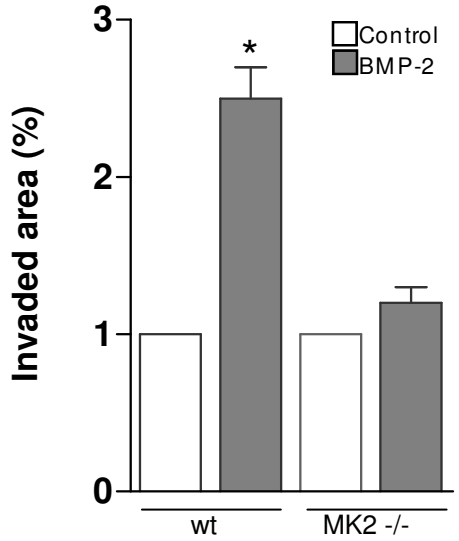


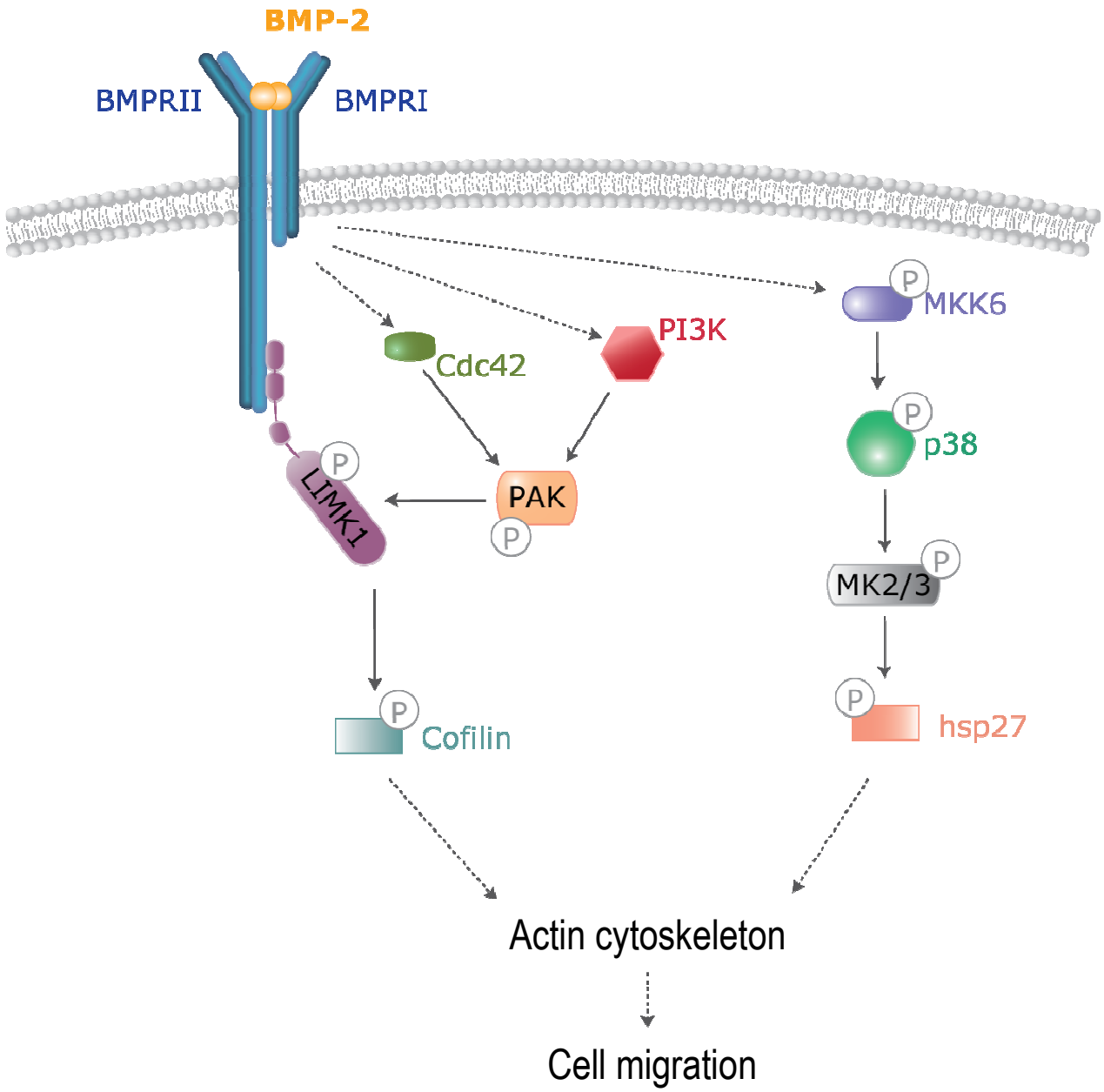




p38-MK2 is also required for BMP-2 induced migration







Gamell C., Osses, N.,Bartrons R., Rückle T.,Camps M., Rosa J.L. and Ventura F.
J Cell Sci. (2008) 121:3960-70.

Acknowledgements

Collaborators:

- Ramon Bartrons
- Ora Bernard
- Montserrat Camps
- Ron T. Hay
- T. John Martin
- Angel Nebreda
- Nelson Osses
- Jose Luis Rosa
- Francesc Viñals

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