



Cardiac and Thoracic Diagnosis & Regeneration



Monocytes Induce STAT3 Activation

in Human Mesenchymal Stem Cells

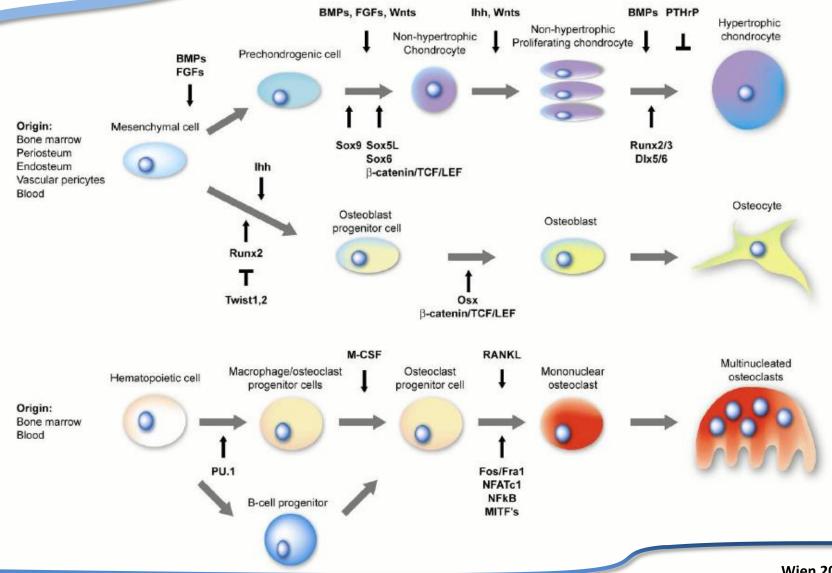
to Promote Osteoblast Formation

Nicolaidou V et al. PloS One. Epub 2012 Jul 3



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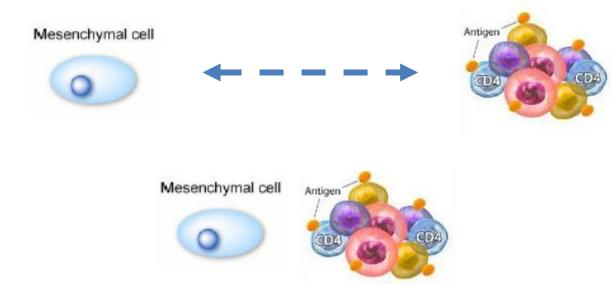


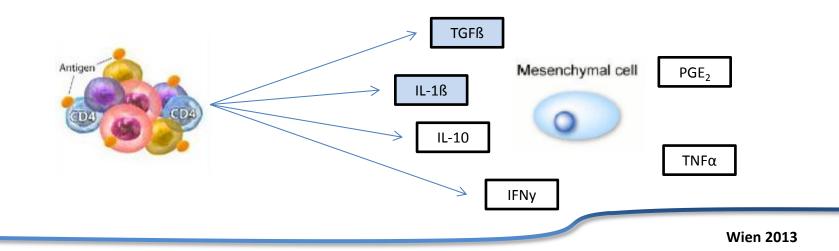
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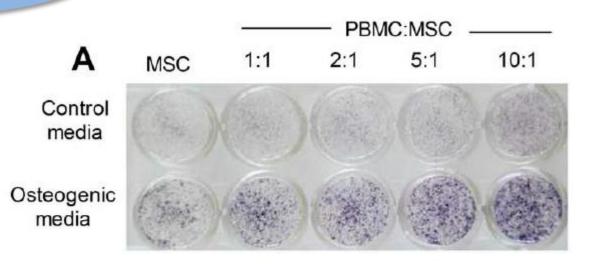


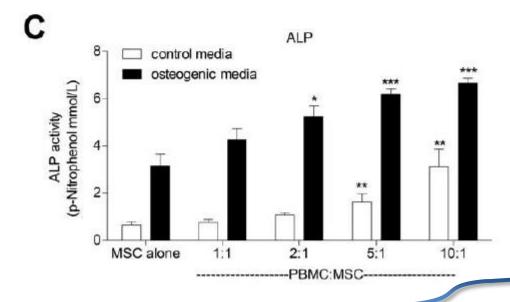


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Alkaline phosphatase





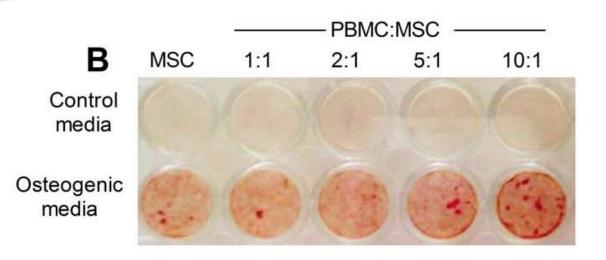


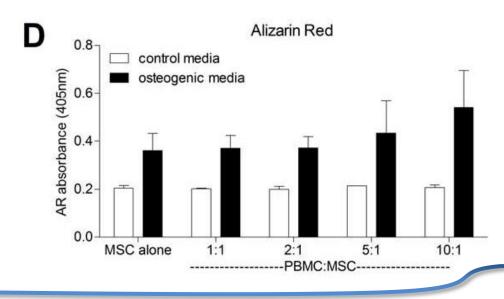


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Alizarin red staining (bone nodule formation)







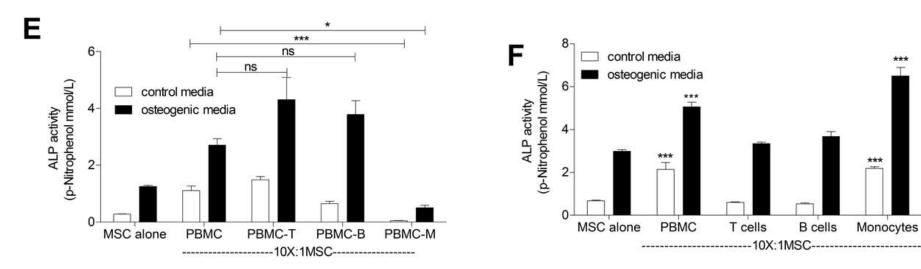
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Cell Depletion



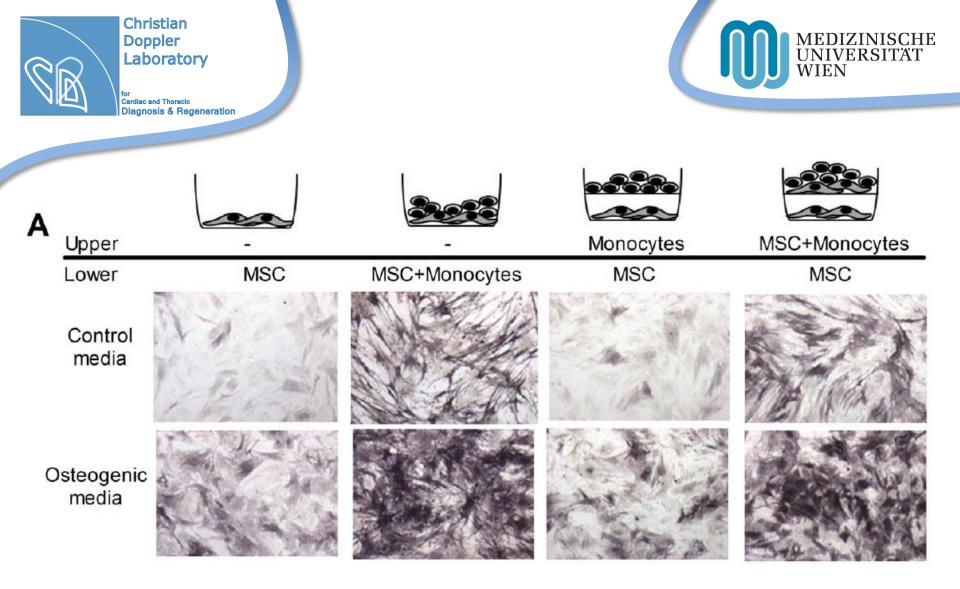


=> monocytes are responsible

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Monocytes

B cells



=> cell contact leads to production of soluble mediators

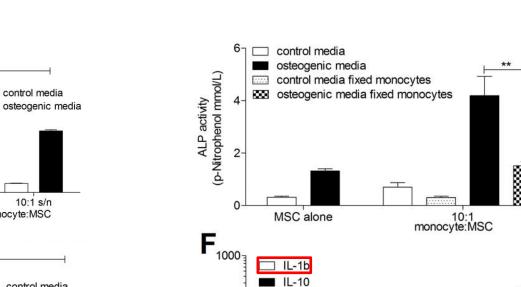


С

2.5

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TNF

MSC alone

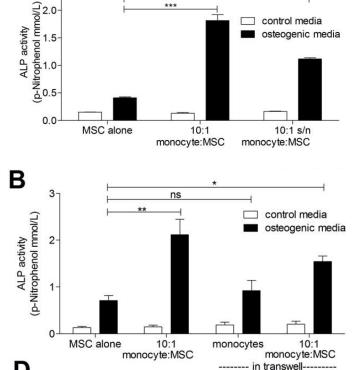
📖 IL-6R

⊞ IL-6 🔳 IL-8

100-

10

pg/ml



control media

=> cell contact leads to production of soluble mediators

10:1 monocyte:MSC

monocytes alone

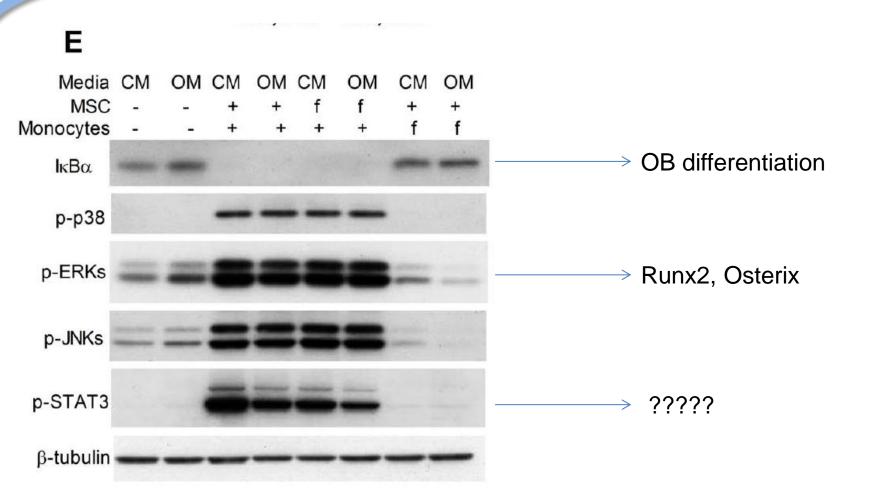
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Signaling Pathways







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STAT 3 Activation



Β Α *** ALP activity (p-Nitrophenol mmol/L) MSC С DN AdGFP 3-2p-STAT3 ns 1 0-STAT3 NSC novirus AGEFP STATSON STATSC С D 3-MSC in osteogenic media ALP activity (p-Nitrophenol mmol/L) MSCs without 10:1 supernatant *** MSCs with 10:1 supernatant AdGFP STAT3C *** 0 AdGFP STAT3DN STAT3C no virus -----Adenovirally-infected MSC------



Christian

Doppler Laboratory

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Microarray Analysis



Illumina human HAT-12 v.30 Expression Bead Chip



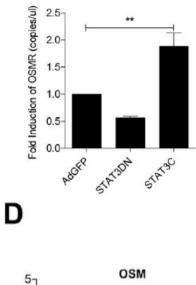
Relation to OB differentiation:

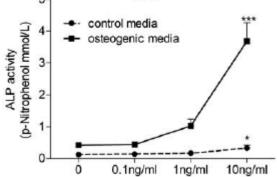
- BMPs
- TGFß
- ALP
- Runx2
- Oncostatin
- Dkk1 (wnt signalling inhibitor)



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Α





Oncostatin M



Ε OSM 10ng/ml 10 20 30 T (min) 0 60 p-STAT3 STAT3 β-tubulin F 10:1 in control media 5 10:1 in osteogenic media ALP activity (p-Nitrophenol mmol/L) 4 3.

10 100 1000 10000 -----OSM Ab ng/ml------

2

1

0

0

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IgG MSC alone

T



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In vivo



G calvaria sections н J p=0.0005 p=0.0028 p=0.0027 200-1.5 PBS ... ** 20calvaria thickness (mm) 150-MAR (µm/day) -50 15 Ir.L.Wi (µm) 100-10 50-5 OSM 0-0.0 0-OSM PBS PBS PBS оśм OSM Inter-label width Calvarial thickness Mineral apposition rate



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Conclusion



- Monocytes induce osteogenic differentiation of human MSCs
- Production of OSM, activation of STAT 3
- Phosphorylation of STAT3 in MSCs upregulates RUNX2 and

ALP expression, downregulates Dkk1