# 研究例 5

## 軟骨形態形成の制御

# Receptors of insulin and IGF complementary mediate signals for the mammalian cartilage organogenesis

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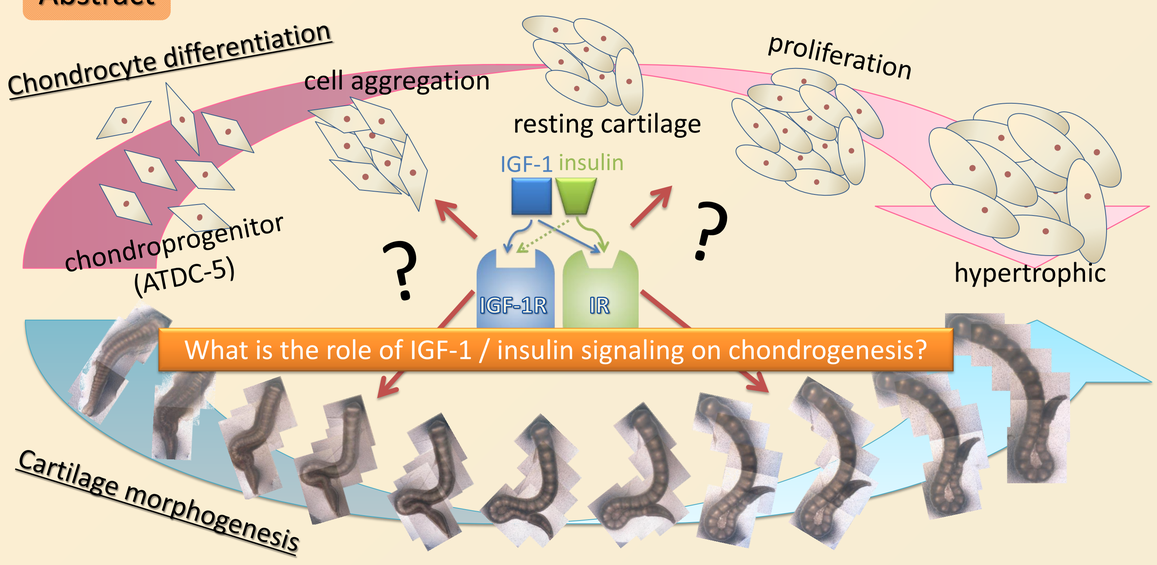
## Abstract




- Insulin induced the differentiation and activated proliferation / motility in chondroprogenitor ATDC-5 cells.
- Attempts were made to clarify the role of IGF-1 / insulin signaling on the cartilage morphogenesis.
  When IGF-1 receptor (IGF-1R) was inactivated,
  - the normal cartilage morphogenesis was prevented in 3D-tailbud, which was partly restored by IGF-1 or insulin.
  - insulin activated downstream more than IGF-1 does.

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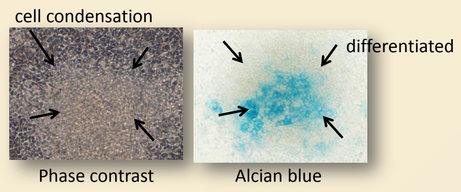
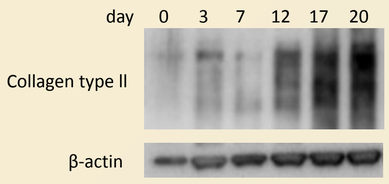
## ATDC-5 cells treated with insulin

Alcian blue staining




The expression of a chondrogenic marker (W. B.)




Insulin induced chondrogenic differentiation via condensation.

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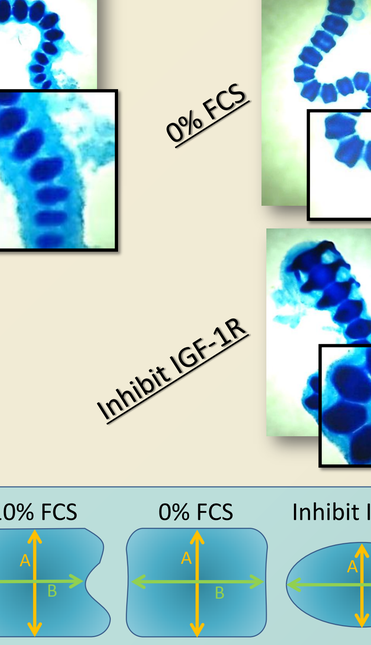
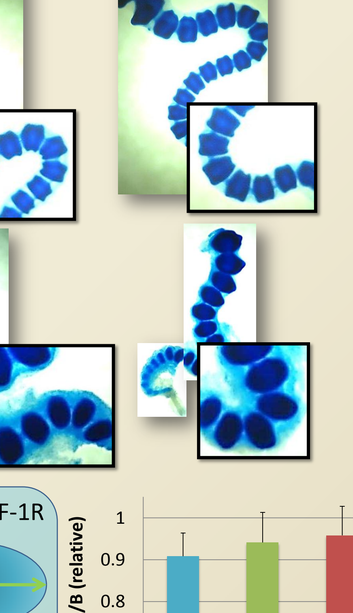
## The effect of insulin on the cell proliferation and the cell motility

Proliferation




Motility




Insulin activated the proliferation and motility, which was considered to be important for morphogenesis.

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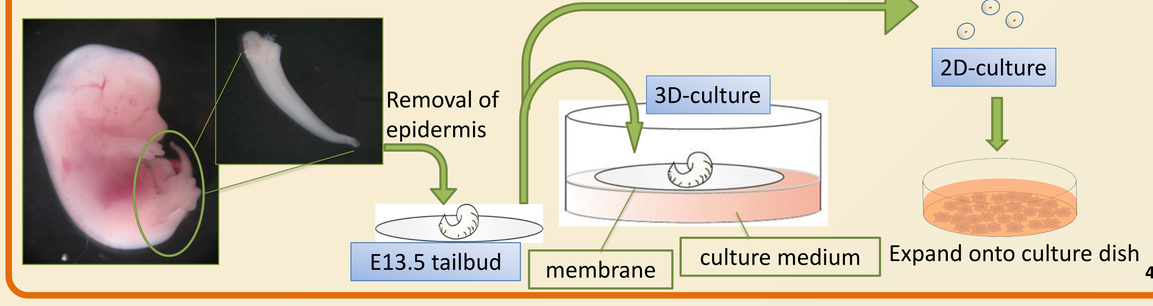
## The culture of E13.5 tailbuds

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## The effect of exogenous IGF-I / insulin on cartilage morphogenesis in 3D-tailbud with dysfunctional IGF-IR




Inhibition of IGF-1R severely depressed the cartilage formation, which was restored either by IGF-1 or insulin.

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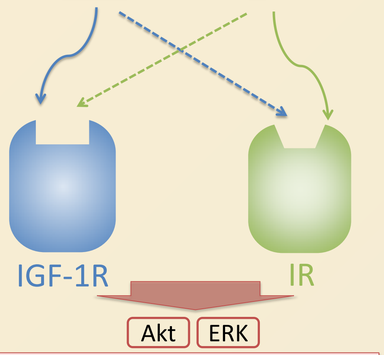
## Interaction of IR / IGF-1R




Both IGF-1 and insulin react to their receptor to activate downstream signalings.

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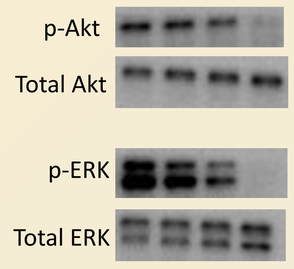
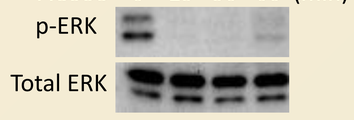
## Inactivation of both IR / IGF-1R

**Dose dependency**




**Time course**




**Response to IGF-1 / insulin**


downstream activation (phospholiration of Akt / ERK)

When both IGF-1R and IR were inactivated:
IGF-1=insulin=control (No signal)

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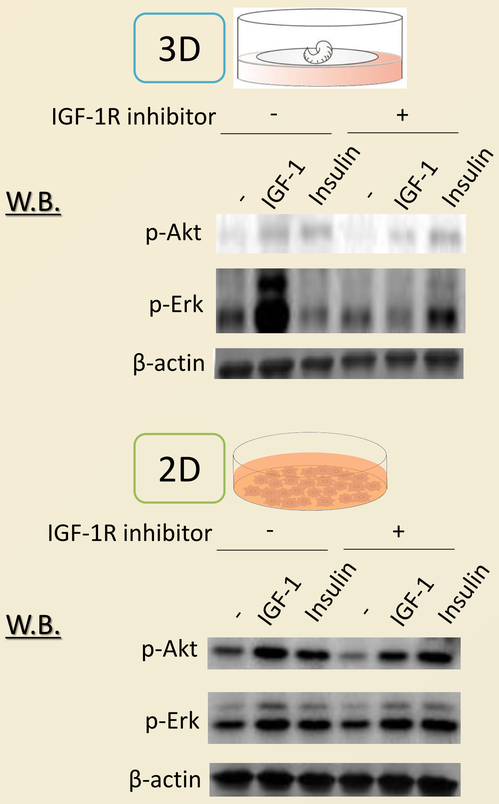
## Effect of inactivation of IGF-1R




downstream activation (phospholiration of Akt / ERK)

- ✓ Ordinary : IGF-1 > insulin >> control (No signal)
- ✓ When IGF-1R was inactivated : insulin > IGF-1 >> control (No signal)

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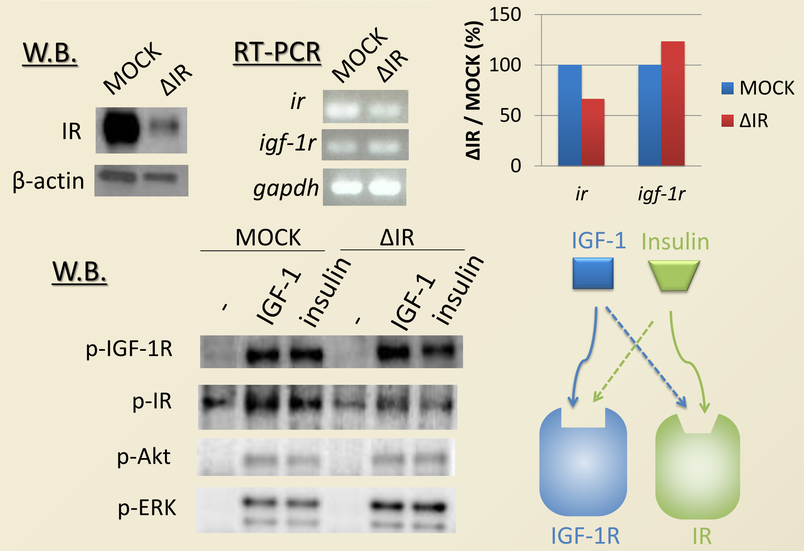
## The effect of IR knockdown




When IR was knock-downed :

- ✓ IGF-1R expression was up-regulated

downstream activation (phospholiration of Akt / ERK)

When IR was knock-downed :

- ✓ IGF-1 = insulin >> control (No signal)

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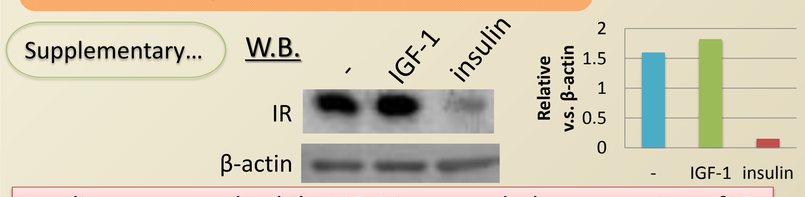
## The regulation of the expression of IR by IGF-1 / insulin

Supplementary...




Insulin suppressed, while IGF-1 increased, the expression of IR.

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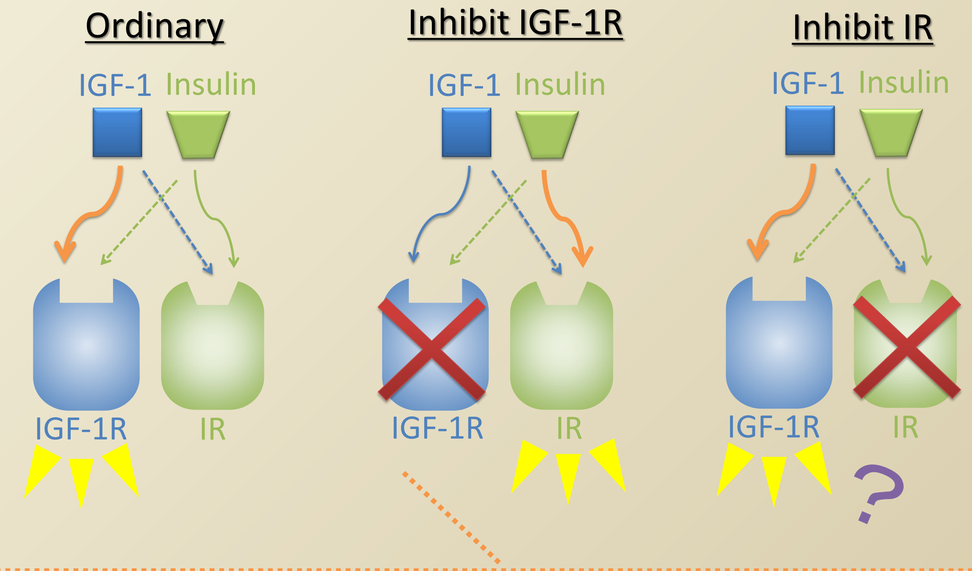
## Conclusion




- ➢IGF-1R / IR signaling plays a key role not only on growth / differentiation but also on the morphogenesis of mammalian cartilage.
- ➢IGF-1 and insulin can bind to both of their receptors to activate the downstream signaling.
- ➢IGF-1R and IR transduce signals in a complementary manner.

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