ANTITUMOR EFFECT OF SCLEROSTIN AGAINST OSTEOSARCOMA

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Introduction

Osteosarcoma

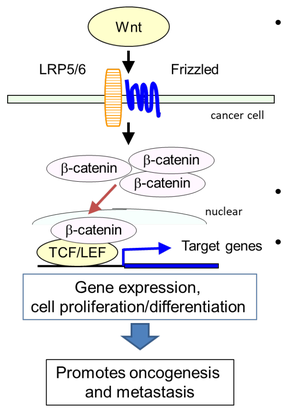
- Ten-year survival rate by combination chemotherapy with MTX, DXR, CDDP, and IFM: over 70%

However,

- Cases wherein preoperative chemotherapy is ineffective: 10-20%
- Five-year survival rate of cases that showed progression at first presentation: 15-24%
- Early recurrences result in poor prognosis. Three-year survival rate: 0%
- There are no therapeutic drugs beyond the aforementioned four-drug combination chemotherapy

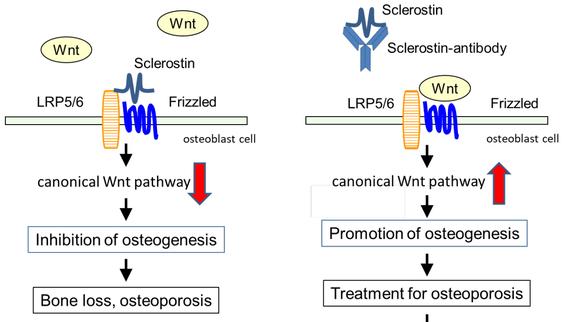
The development of new therapeutic drugs remains imperative

Wnt signaling



- Signaling pathway that regulates a wide range of biological events such as development, growth, stem cell maintenance/ differentiation, and homeostatic maintenance
- There are canonical (β-catenin) and noncanonical pathways
- The canonical pathway promotes oncogenesis and metastasis of various cancers

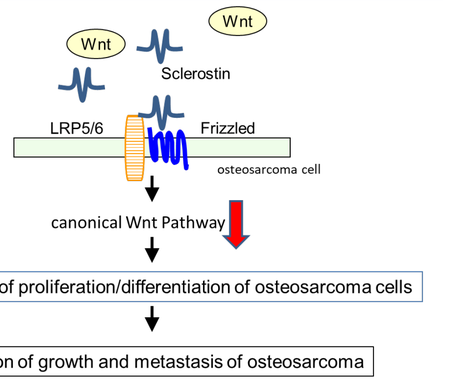
Sclerostin & its antibody



- Sclerostin is mainly secreted by osteocytes
- Binds to LRP 5/6 and suppresses the canonical Wnt pathway

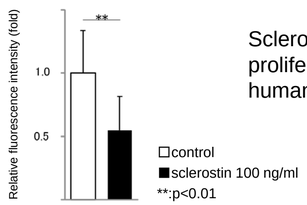
Hypothesis

Sclerostin inhibit growth and metastasis of osteosarcoma !?



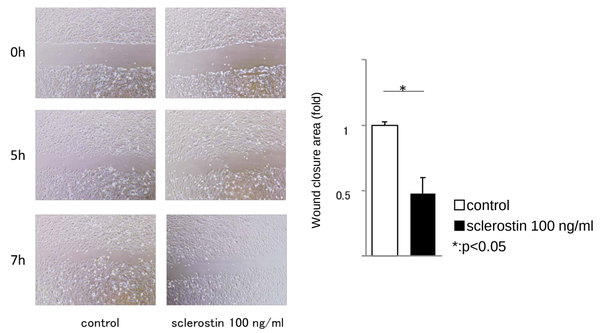
Methods & Results

alamarBlue Assay



Sclerostin suppresses the proliferative capacity of the human osteosarcoma cell line

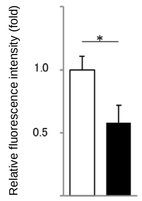
Scratch Assay



Sclerostin suppresses the proliferative and migratory capacity of the human osteosarcoma cell line

Methods & Results

Migration Assay



Sclerostin suppresses the migratory capacity of the human osteosarcoma cell line

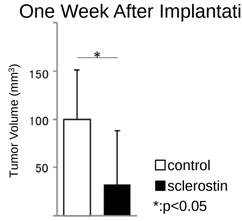
Creating Mice Models for Osteosarcoma

Mouse model for mouse osteosarcoma	Mouse model for human osteosarcoma
Mouse osteosarcoma cell line LM8, a strain with highly metastatic potential to the lung	Human osteosarcoma cell line 143 B
Four-week-old C3H/HeSlc mice of same strain (Japan SLC, Inc.)	Four-week-old BALB/cSlc-nu/nu nude mice (Japan SLC, Inc.)

1×10^6 cells were implanted subcutaneously

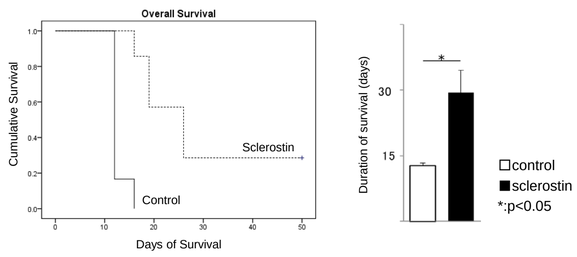
Changes in Tumor Size due to Sclerostin Administration

Dosage: 80 ng/g body weight
Dose interval:
once per day for seven days
Route of administration:
Intraperitoneal administration



Sclerostin suppresses tumor growth of osteosarcoma

Changes in Survival Time due to Sclerostin Administration



Sclerostin extends the survival time of osteosarcoma mice models

Discussion

- Enhancement of canonical Wnt signaling exacerbates the prognosis of osteosarcoma

  Hoang BH. Int J Cancer. 2004

- Antitumor effect of Wnt inhibitor (Dkk-3, WIF-1, SFRP, etc.) against osteosarcoma was reported

  Lin CH. Sarcoma 2013
  Kansara M. J Clin Invest. 2009
  SHI Y. Acta Pharmacol Sin 2007

An antitumor effect of sclerostin was observed against osteosarcoma

- It is highly probable that sclerostin also exerts an antitumor effect by inhibiting the Wnt pathway
- Verification of the actual mechanism is needed

- Specificity of sclerostin to bone

  van Bezooijen RL. J Exp Med. 2004.
  Moester MJ. Calcif Tissue Int. 2010.
  Weivoda MM. Curr Osteoporos Rep. 2014.

- On the safety of sclerostin administration
  - Mice with overexpressed sclerostin became osteoporotic

    Winkler DG. EMBO J, 2003
  - There are no reports on the systemic effects of overexpression or sclerostin administration

No serious complications were observed on mice models with sclerostin

- Pharmacokinetics during sclerostin administration is unknown
- An evaluation of complications is necessary for future research, including osteoporosis
- Anticipation for its advantages in terms of safety due to specificity to bone

Conclusion

- We examined the antitumor effect of sclerostin, a Wnt inhibitor with high specificity to bone, on osteosarcoma
- Both in vitro and in vivo examinations confirmed significant antitumor effects
- Since sclerostin is not a cytocidal agent, an investigation on its combined clinical use with existing anticancer agents such as doxorubicin is necessary for future research

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