Prostate cancer and Wnt pathway

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Wnt pathway

• **Int-1** (cellular oncogene): mouse mammary tumor virus induced tumor
  
  *Nusse R and Varmus HE, 1982 cell*

• **Int-1 = wingless** (Elucidate through analysis of wingless signalling-*drosophila* homolog)
  
  *Rijsewijk et al, 1987 Cell*

• **Wnt=Int-1 + Wingless(Wg)**
  
  *Nusse et al, 1991 cell*

• **Wnt protein- large family of cysteine-rich secreted ligands**
  
  [http://www.stanford.edu/group/nusselab/cgi-bin/wnt/](http://www.stanford.edu/group/nusselab/cgi-bin/wnt/)
Stanford University
Dr. Roel Nusse group
http://www.stanford.edu/group/nusselab/cgi-bin/wnt/
What is Wnts pathway?

- Wnt proteins,
  1. cysteine-rich-secreted ligand glycoproteins
  2. Autocrine or paracrine effects
  3. Organ development, tissue patterning, cell fate and proliferation, movement
  4. activate at least three distinct pathways:
     - Canonical (b-catenin-dependent),
     - Non-canonical -Ca2+, or planar polarity.
Regulation of β-catenin levels and translation
Canonical Wnts pathway

• By Wnt1, Wnt2, Wnt3a, Wnt10a

• **Dependent β -catenin**

• Main protein: β –catenin

① is degraded by GSK3b

② Structural adaptor protein: actin + cadherin
Wnt3a and β-catenin by IF

LNCaP

Con

Wnt3A

22RV1

Con

Wnt3A

AR  β-catenin  DAPI  Merge
Non-canonical Wnts pathway

• Via Frizzled and Ror1 or Ror2 receptor
• Via G protein : control of Ca2+ fluxes and phosphatidyl inositide metabolism
• Initiate the RhoA, JNK (C-jun N-terminal kinase), calcium signaling pathway
• Maybe play roles in guiding mesenchymal stem cell fate
• Wnt4, Wnt5a, Wnt11
Figure 1. An overview of Wnt-5a signalling. (A) Wnt-5a can activate PCP through a process dependent on Roh A and possibly Roh B leading to the control of cellular movement. (B) Wnt-5a uses numerous signalling molecules leading to the release of Ca\(^{2+}\) resulting in various cellular effects including cell movement and inhibition of the canonical Wnt signalling pathway. (C) Wnt-5a can bind the ROR-2 receptor activating JNK and the cytoskeleton as well as inhibiting β-catenin/TCF dependent transcription. (D) Wnt-5a can inhibit β-catenin/TCF-dependent transcription through Shia-1. (E) In the presence of FZ4 and LRP-5, Wnt-5a can activate β-catenin/TCF-dependent transcription. (F) Wnt-5a can activate PKA, which in turn can inhibit GSK-β to promote β-catenin/TCF-dependent transcription. Figure adapted from Semenov et al. (2007).
Wnt5a protein activates β-catenin signaling depending on receptor context

**Normal prostate gland development and Wnt5a in rats**

- Wnt5a is essential for normal prostate development where its regulations bud outgrowth, ductal elongation, braching, cell polarity and lumenization.

_Huang L et al, 2009 Dev Biol_
Wnt pathway and prostate cancer?
Mutation of $\beta$-catenin in prostate cancer

- Exon 3 of the $\beta$-catenin gene CTNNB1 → site of phosphorylation of $\beta$-catenin → stabilization of $\beta$-catenin
  

- APC mutation
  
  Gerstein et al. 2002 Genes Chromosomes Cancer
Wnt signalling
Alteration in expression of β-catenin in prostate cancer

* Location change of β-catenin: increasing in cytoplasm and nucleus

Chesire et al, 2002 oncogene
De la Taille et al, 2003 clinical cancer res
Chen et al, 2004 Cancer
Wnt pathway may contribute to progression of prostate cancer to androgen independence

De la Taille et al, 2003 clinical cancer res
Chen et al, 2004 Cancer

Fig. 4 Increase of β-catenin abnormal (cytoplasm/nucleus) distribution according to the GS in prostate cancer (n = 122, patients with localized PrCa).
Expression of cytosolic $\beta$-catenin

A

Membrane weak and cytosol weak
Membrane moderate and cytosol weak
Membrane strong and cytosol strong

B

\[ \text{Expression: } \bar{x} \ (SE) \]

C

Disease progression

D

1' Gleason grade

E

Preoperative PSA

F

Bone metastasis

ANOVA or student’s t-test, Expression: Mean (SE)

\( \chi^2 \) test, p=0.001

p=0.006

p=0.001

p=0.006

p=0.001

p=0.001
β-catenin and androgen receptor

• Nuclear β-catenins are an activator of the androgen receptor
• β-catenin significantly enhances androgen-stimulated transcriptional activity by the AR and diminished its antagonist
• β-catenin/TCF-related transcription is inhibited by androgen treatment

→ β-catenin may link development of androgen insensitivity

Truica CI et al, 2000 Cancer Res
Culig Z et al, 1998 prostate
Chesire DR et al. 2002 oncogen
The androgen receptor can signal through Wnt/beta-Catenin in prostate cancer cells as an adaptation mechanism to castration levels of androgens.

Schweizer L et al, 2008 BMC Cell Biol
WNT signaling regulates self-renewal and differentiation of prostate cancer cells with stem cell characteristics

Bisson I et al, 2009 Cell res
Wnts signaling in cancer

- Colon cancer, prostate cancer: β-catenin mutation or increased cytosolic/nuclear β-catenin
- Transcription factor c-Myc, cell cycle regulatory protein
  cyclin D1 ↑
What is the role of Wnts and BMPs pathways in bone metastasis?

• The most common site of CaP metastasis is the bone with up to 84% of patients demonstrating skeletal metastases.

• The majority of cancers, such as breast and myeloma, produce areas of bone lysis (osteolytic lesions) when they metastasize to bone.

• Although there is consistently an osteolytic component to CaP bone metastases, they are typically characterized radiographically by areas of increased bone production (i.e., osteoblastic).
Wnt pathway and bone metastasis
Prostate cancer induces bone metastasis through Wnt-induced bone morphogenetic protein-dependent and independent mechanisms.
Take home Message

✓ **Wnt pathway** is the important component of prostate cancer progression and tumorigenesis
✓ A variable chemoprevention agents have an effect on the **Wnt / β-catenin pathway**
  - folic acid, Cyclooxygenase inhibitors, NSAIDs
  - β-catenin-TCF/LEF transcription complex inhibitor
  - APC function mimicking agent
Thank you very much for your attention