In vitro studies of the microenvironmental factors responsible of the proliferation and aggressiveness of desmoid tumor cells

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Genetic and epigenetic alterations of the Wnt/β-catenin signaling pathway

Microenvironmental factors:
- Inflammation
- Growth factors
- Hormones

Activation of aberrant fibroblasts

Excessive accumulation of Extracellular Matrix Proteins (ECM)

Fibrous tissue

Desmoid Tumor

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IL1-β, TNF-α and TGF-β have a pro-proliferative effect in desmoid tumor cells growth

Microenviromental factors tested:

- Growth factors
- Hormones
- Inflammatory factors

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TGF-β increments the proliferation of desmoid tumor cells

One hour of TGF-β treatment is sufficient to promote desmoid tumor cells proliferation
The proliferation of desmoid tumor cells is confirmed by the Ki-67 positive-nuclei.

Cyclin D1 is expressed in all desmoid tumor cells regardless of treatment time points.

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TGF-β is a multifunctional cytokine

TGF-β affects numerous biological pathways:

- Inflammation and fibrosis
- Cells proliferation and migration
- Wound healing
- Regulation of embryogenesis
- Immunity
- Carcinogenesis

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TGF-β is a key driver of fibrosis

• TGF-β regulates the activation of fibroblasts and their differentiation into myofibroblasts
• TGF-β stimulates the extracellular matrix production
• Additional pathways are important for the transmission of the profibrotic effect of TGF-β

Wnt/β-catenin and TGF-β pathways interaction

Interactions between Wnt/β-catenin and TGF-β pathways induce the alpha-SMA expression, marker of the myofibroblasts differentiation
(Zhou et al., J. Biol. Chem., 2012)

Interaction between Wnt/β-catenin and TGF-β pathways regulates cutaneous wound size, in mouse model (Cheon SS. et al., Faseb J., 2006)
TGF-β induces the differentiation of desmoid tumor fibroblast cells in myofibroblast cells.

Alpha-Smooth Muscle Actin (α-SMA) is highly expressed in DF cells and it showed a fibrillar staining, peculiar of myofibroblast cells.
Normal and desmoid tumor cells express high level of Fibronectin and MMP9 when treated with TGF-β

TGF-β induces vimentin fibrillar expression in desmoid tumor cells

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TGF-β induces oligomerization of TGF receptor and activates the Smad pathway.

Normal cells and desmoid tumor cells show similar expression level of the TGF-β receptor, TGFBRII.
TGF-β activates Smad-dependent pathway

Smad 2/3 complex is largely expressed in the cytoplasm and in the nucleus of desmoid tumor cells.

Smad 4 is highly expressed in the nucleus of untreated or shortly TGF-β treated desmoid tumor cells, while it is weakly expressed in the cell cytoplasm.

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CONCLUSIONS

The alteration of Wnt/β-catenin pathway in desmoid tumor is modulated by the interaction with microenvironmental factors

TGF-β has a key role in the desmoid tumor cells proliferation

TGF-β regulates the activation of desmoid fibroblast-like cells and their differentiation into myofibroblasts

TGF-β activates Smad pathway in desmoid tumor cells

The Wnt/β-catenin and TGF-β pathways cross-talk might be involved in desmoid tumor cells proliferation and differentiation