

A systematic review of the role and expression of TGF-β in uterine fibroids

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Background

Fibroids are:

- Benign tumours made up of smooth muscle cells and dysregulated extracellular matrix (ECM)(Fig.1), affecting 70-80% of premenopausal women.
- One of the largest indications for hysterectomies in the UK.
- Better understanding of pathogenesis needed for medical treatment methods

Transforming Growth Factor-β (TGF-β) is:

- A polypeptide involved in tissue fibrosis, immune system modulation, cell growth and differentiation.
- 3 isoforms TGF-β1, -β2 and -β3 with variable roles in uterine fibroid pathogenesis.
- Significant evidence showing overexpression in fibroids, but function unknown**

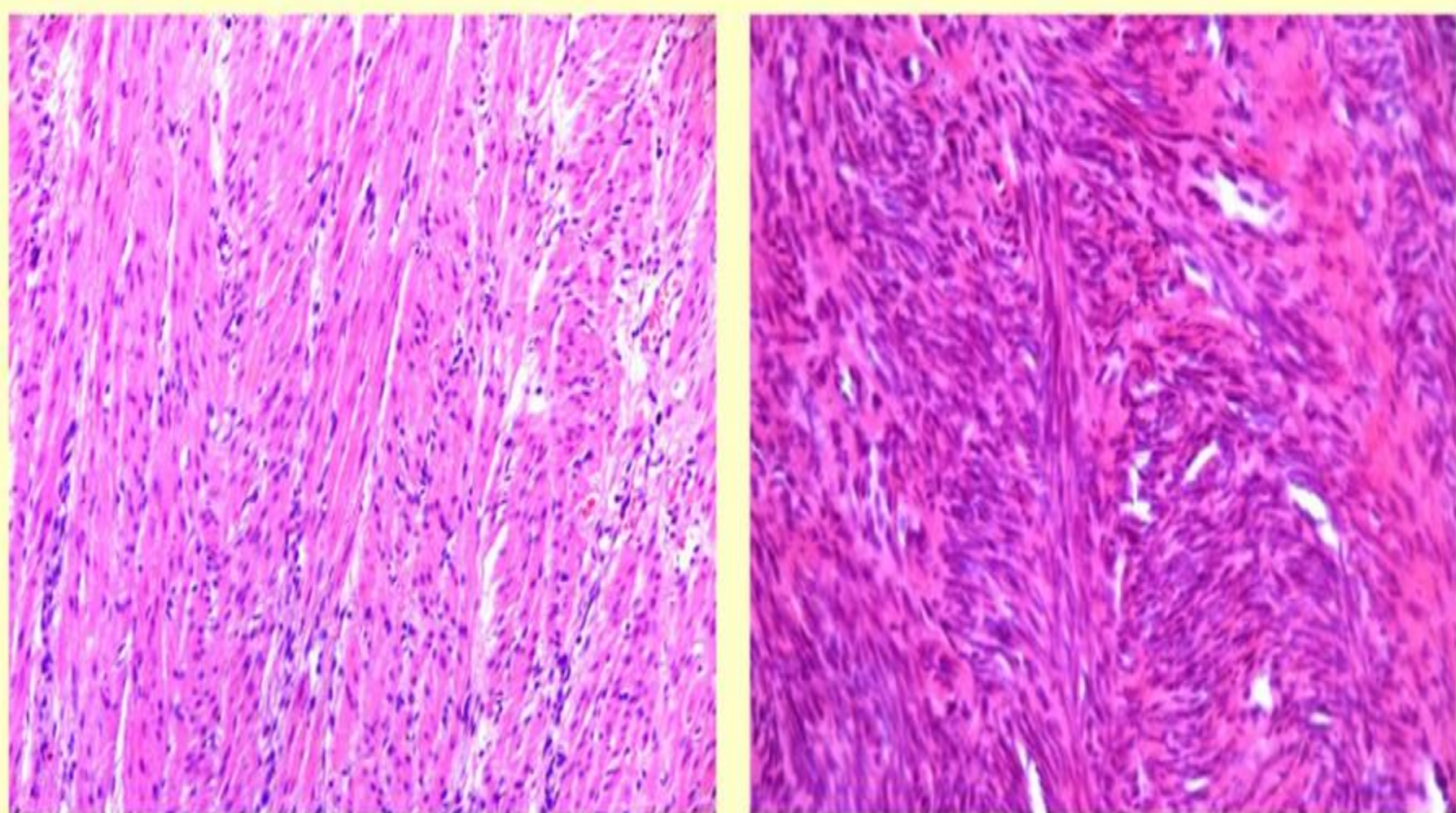


Fig 1. Comparison of healthy myometrium vs fibroids, shows irregular, disorganized smooth muscle cells with more collagen and fibroblasts.

Results

Isoform expression

TGF-β1: 8 studies showed no or reduced expression; 4 found overexpression

- TGF-β1 plays a vital role in fibrosis. At **higher concentrations has inhibitory effect** suggesting proliferative effect in early fibroid development.
- This is further proven by studies that find in larger fibroids there is reduced expression of TGF-β1.
- This may conciliate the contradictory literature about its expression.

TGF-β2: No significant difference found.

- Unaffected by treatment with Ulipristal acetate suggesting lack of modulation by androgens.

TGF-β3: 18 studies found overexpression (Fig 3)

- Major role in ECM production through upregulation of fibronectin, MMP, collagen and proteoglycans (Fig 4)
- TGF-β3 expression is modulated by **ovarian hormones, Wnt/β-Catenin pathways, MED12 mutations and ECM related microRNAs** (Fig 5)
- TGF-β3 is the main isoform involved in fibroid pathogenesis**

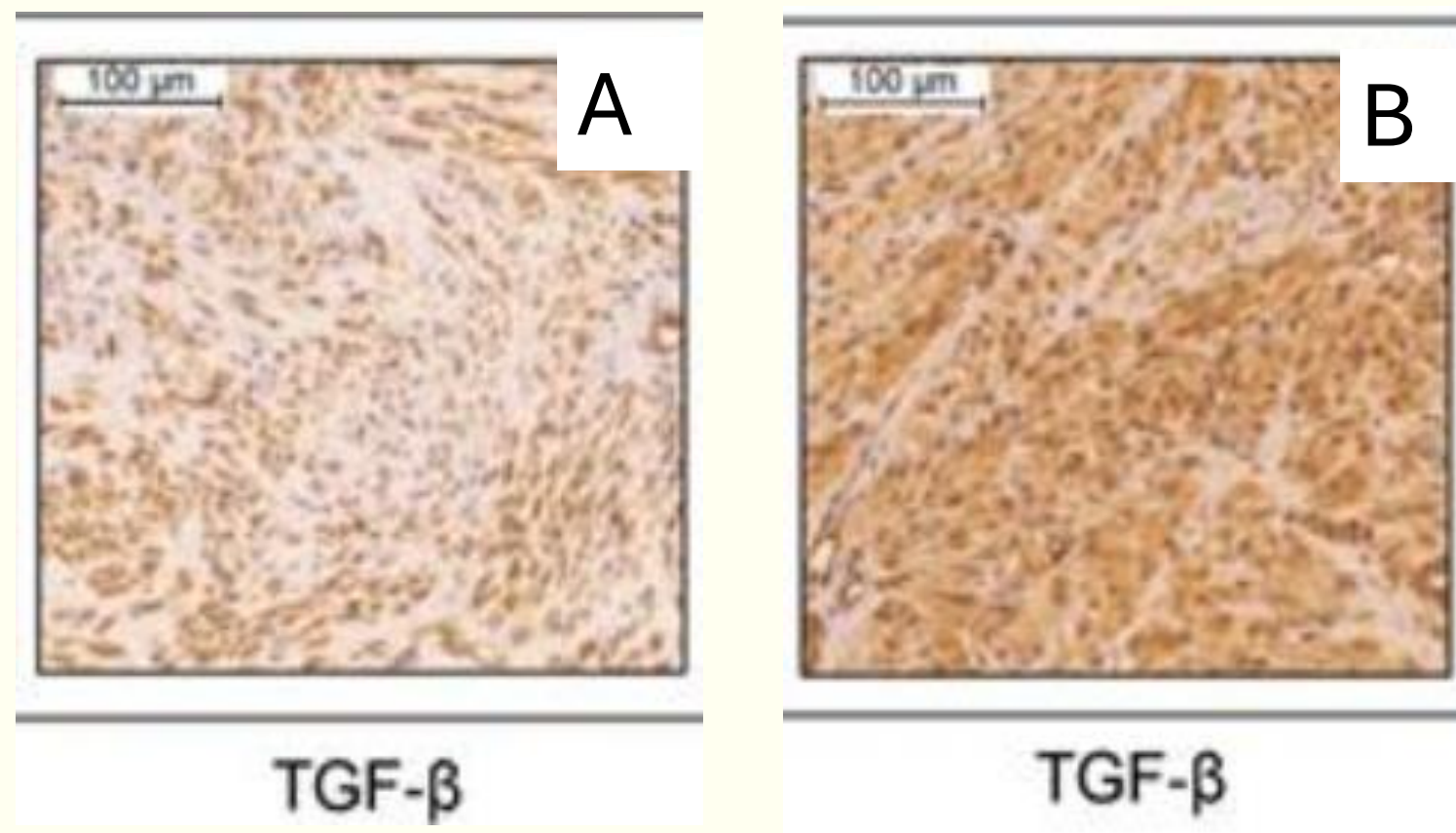


Fig. 3. Immunohistochemical stain comparing the expression of TGF-β3 expression in A (healthy myometrium) vs B (uterine leiomyoma).

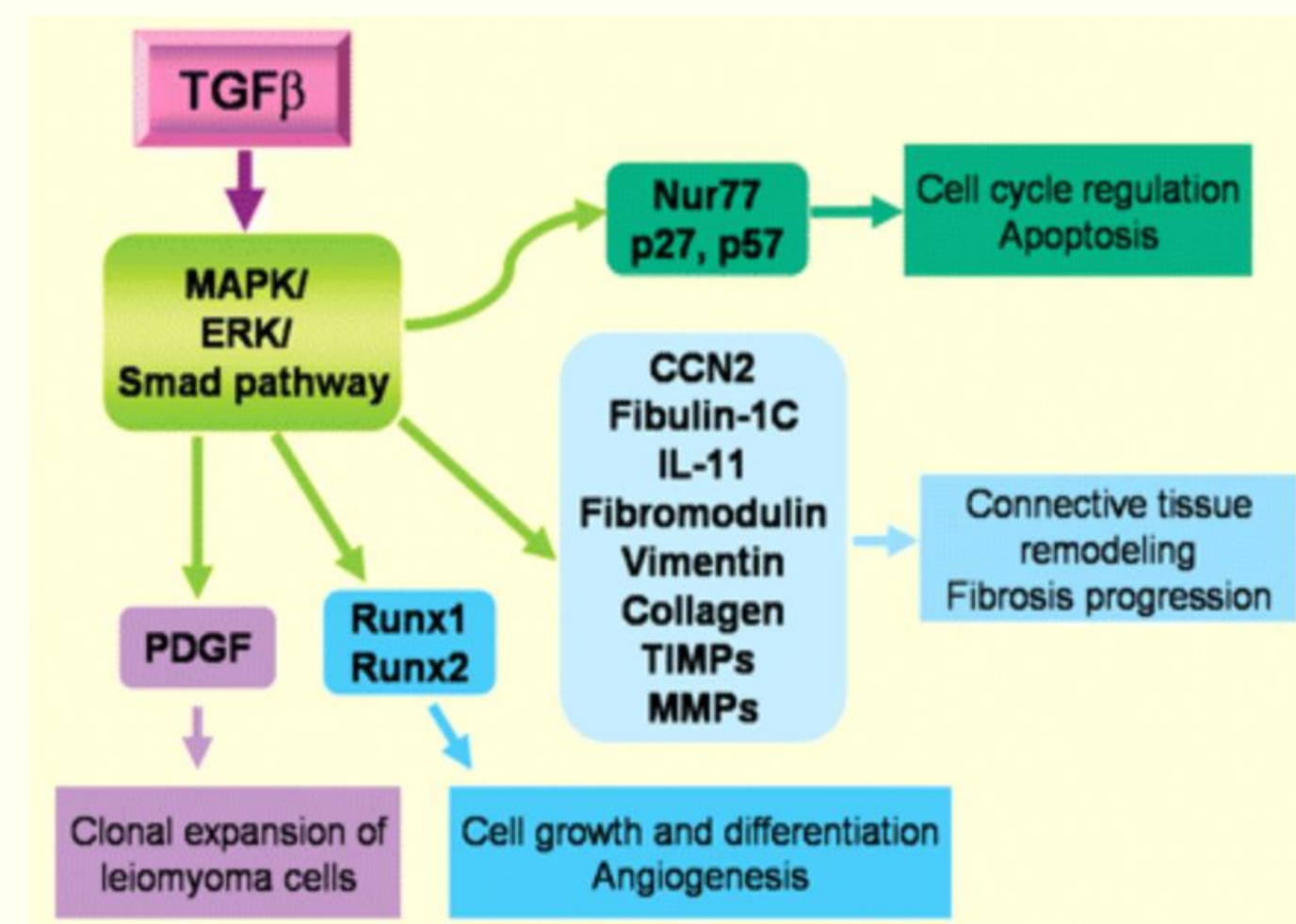


Fig. 4. Flow chart showing the non-Canonical downstream signaling pathways of TGF-β3 in fibroid development.

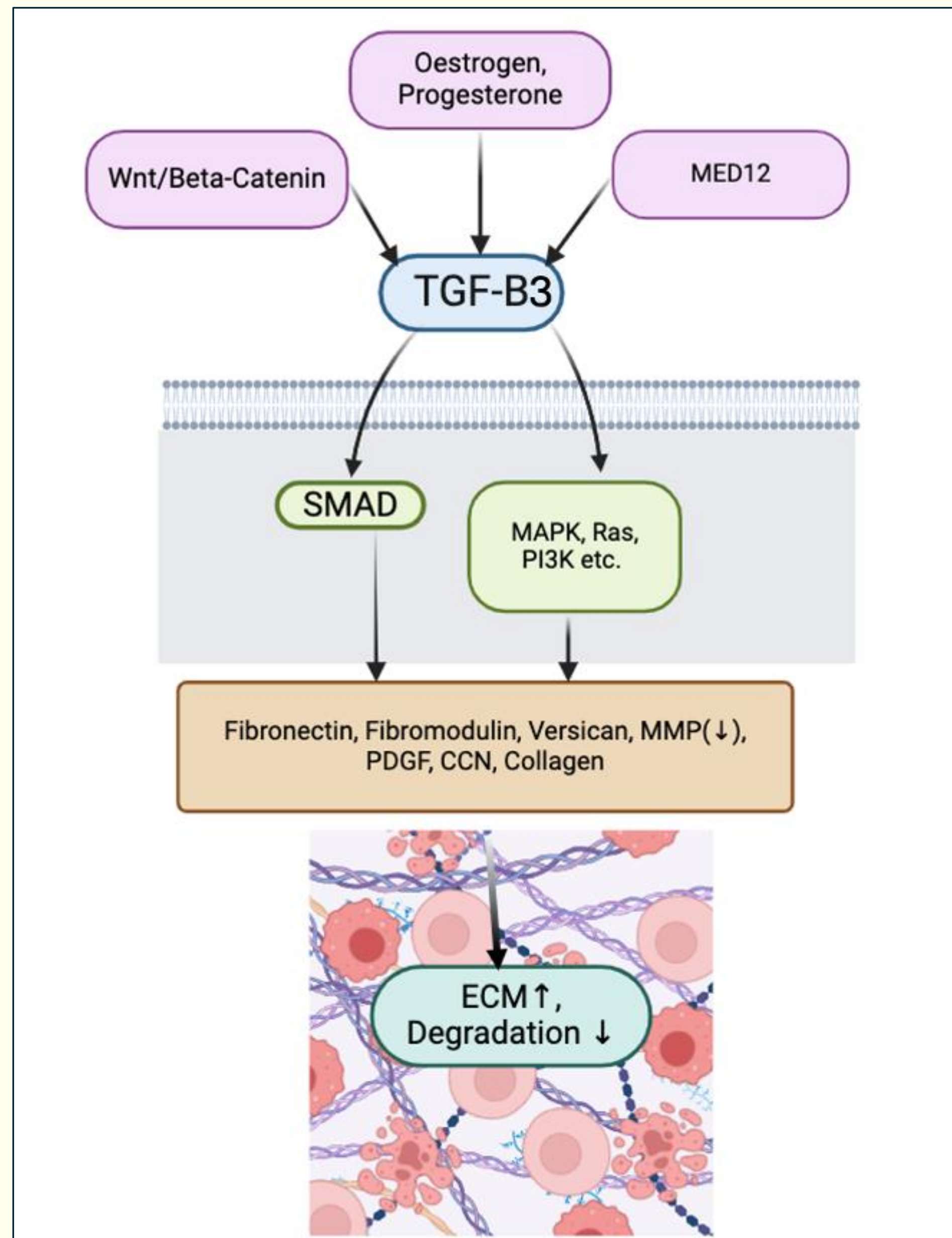


Fig 5. Summary of the role of TGF-β3 in Fibroid development.

Hypothesis and Aims

TGF-β3 plays a central role in the fibrotic processes in fibroid development. To assess this, we need to answer:

- To what extent are each TGF-β isoform over-expressed in uterine leiomyoma vs healthy myometrium?
- How does this overexpression/ under-expression relate to its function in fibroid development?

Methods

A systematic search was conducted across 3 databases, **PubMed**, **Embase** and **Medline**. Search terms were synonyms of 'TGF-β' and 'Uterine fibroids'.

Following removal of duplicates and the use of specific exclusion and inclusion criteria a total of **28 studies** were found

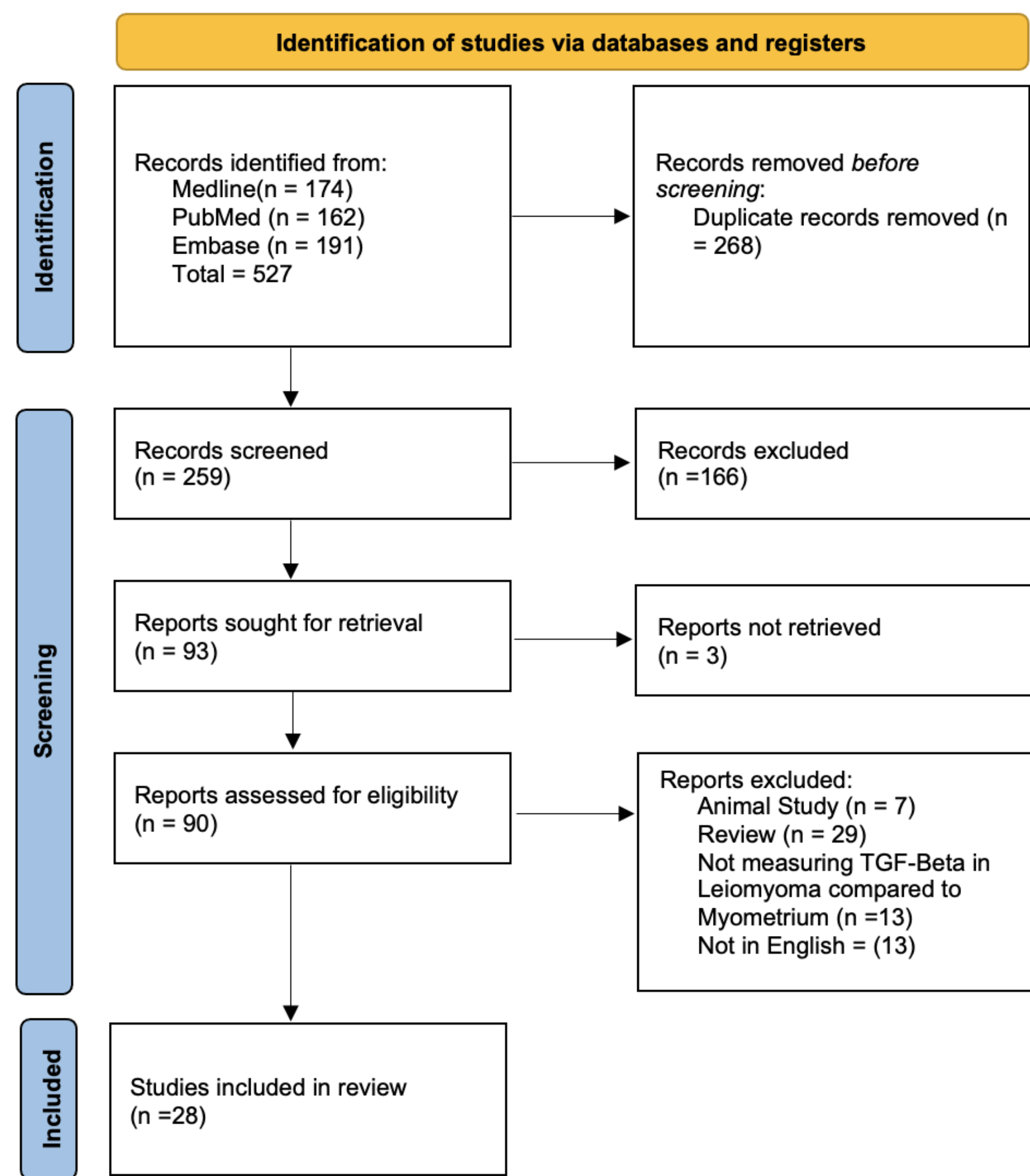


Fig 2. PRISMA flowchart showing inclusion criteria; measuring endogenous TGF-β in fibroids vs healthy myometrium. Exclusion criteria; Animal study, Review, Not measuring TGF-β in leiomyoma compared to myometrium, not in English. Search terms were synonyms of 'TGF-β' and 'Uterine fibroids'.

Therapeutics

- Vitamin D deficiency correlates with fibroids.
- Ulipristal acetate and Vitamin D were linked to a reduction of TGF-β3 activity** via Canonical and non-Canonical pathways.
- Vitamin D used in combination with Ulipristal acetate reduced TGF-β3 by more than 50%.

Biomarker potential

- Two studies measuring TGF-β3 in serum suggest its use in diagnosis and monitoring.

Conclusion and Future Work

Conclusions

- TGF-β3 is upregulated in leiomyomas leading to cell proliferation and ECM production through the Canonical and Non-Canonical pathways
- TGF-β3 is regulated by ovarian hormones, Wnt/β-Catenin pathway and MED12 mutations.
- UPA and Vitamin D are promising non-surgical ways of managing fibroids.

Future Work

- Clarification of the role of the different isoforms
- The Canonical and Non-canonical signaling pathways mediating the effects of the isoforms
- Whether the inhibition of TGF-β3 (either direct or indirectly) will be of therapeutic value.