Molecular Subclass of Uterine Fibroids Predicts Response to Ulipristal Acetate Treatment

Åsa Kolterud1, Niko Välimäki2, Heli Kuisma2, Joonatan Patomo2, Netta Mäkinen2, Jaana Kaukomaa2, Kimmo Palin2, Eevi Kaasinen2, Auli Karhu2, Annukka Pasanen3, Raif Büttow3, Oskari Heikinheimo3, Helena Kopp Kallner1,2, and Lauri Aaltonen1,2

1. Karolinska Institutet, Sweden 2. University of Helsinki, Finland 3. University of Helsinki and Helsinki University Hospital, Finland 4. Danderyd Hospital and Karolinska Institutet, Sweden

Subclass as treatment predictor
The results from this retrospective study show for the first time that genetic uterine fibroid (UF) subclasses influence drug treatment response. Our findings highlight the need of taking UF molecular subclass into account when developing and evaluating current and future therapies.

Aim
To investigate if the two most common UF subclasses, driven by aberrations in MED12 (70%) and HMGA2 (15%) genes respectively, influence treatment response to the selective progesterone receptor modulator ulipristal acetate (UPA).

Study material and work flow
Total patients retrospectively reviewed (SWE+FIN) n=1666

\[ \text{UPA treated (≥3 months before surgery)} \quad n=162 \]

Sufficient info on UPA effect on UF size m=84 (105 UFAs)

Assessment of treatment response

Very Good: n=27

Good: n=22

No Response: n=56

Screened for MED12 mutations and HMGA2 overexpression (blinded to treatment response)

MED12 UFs more responsive to UPA treatment
MED12 UFs were found to have 4.8 times higher odds to UPA induced size reduction compared to HMGA2 UFs (95% confidence interval (CI) 1.47-15.6; P=0.0093; VGR/GR versus NR). Initial UF size or number of UFs did not explain the observed difference.

Subclass specific differences in progesterone receptor signaling
A) Progesterone receptor (PGR) expression in normal myometrium (n=162), HMGA2 UFs (n=44), MED12 UFs (n=42) and UFs wild type for HMGA2 and MED12 (n=175). Y-axis variance stabilized gene counts. B) Average Cpg methylation at PGR binding sites in normal myometrium (n=96), HMGA2 UFs (n=28), MED12 UFs (n=13) and UFs wild type for HMGA2 and MED12 (n=61). C) Principal component analysis (PCA) of 48 progesterone related genes.

Potential underlying mechanisms
Existing RNA-sequencing and DNA-methylation data derived from MED12 and HMGA2 UFs (Berta D. et al. Nature 2021, 596:398-403) was used to explore potential differences in progesterone signaling, extracellular matrix composition and apoptosis.

Distinct extracellular matrix but not apoptosis expression signature

Principal component analysis (PCA) of A) 84 extracellular matrix related genes and B) 90 apoptosis related genes.