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The preterm labor associated ADAMTS2 gene is induced by glucocorticoids

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In their study of the maternal blood leukocyte transcriptome at the time of preterm labor Paquette *et al.* (1) report on a 5-fold increase of the *ADAMTS2* transcripts as compared to term labor and go on to suggest it may be a clinically useful biomarker for this condition. The authors considered the possible impact of glucocorticoids (GC), which are given before preterm but not term delivery and they addressed this by analyzing the GSE61881 GEO dataset, which we published alongside a paper on the response of macrophages to GC (2). In their analysis of our data Paquette *et al*. do not mention the response of *ADAMTS2* under "Results" but they imply that ADAMTS2 does not change with GC. However, in their Table S4, which compiles FDR values, *ADAMTS2* is listed as a responder gene and our published analysis of the same data (GSE61881) also clearly demonstrates that *ADAMTS2* is strongly induced as given in the table below:

Symbol	log2 fold change	Adjusted p-value (Benjamini-Hochberg)	Time (h)
ADAMTS2	2.019	4.67E-04	10
ADAMTS2	4.836	4.52E-09	24

Furthermore, looking at human blood monocytes in another in-vitro study we reported earlier on a >100-fold induction of *ADAMTS2* by GC in a dose and time dependent manner (3). Incidentally this study was based on the observation of an induction of *ADAMTS2* mRNA expression in monocyte-derived macrophages obtained from patients, who had received oral treatment with GC (GEO GSE8608) before donating blood.

The findings by both Jubb *et al.* and Hofer *et al.* do not support the conclusion by Paquette *et al.* that "Our results suggest PM (peripheral monocyte) or WB (whole blood) ADAMTS2 expression could also serve as a non-invasive clinical test of sPTL (spontaneous preterm labor)". Rather the data show that *ADAMTS2* is a gene, which is induced by GC with slow kinetics and a long half-life such that the effect of the drug, given before preterm delivery, is still seen hours and days after application.

In the report by Paquette et al (1) the influence of GC on the genes differentially expressed in preterm labor is suggested to be limited. However, there are several genes that Paquette *et al.* - in their analysis of our data - list as being 'non-responders' to dexamethasone, which are, in fact, strongly induced by glucocorticoids, e.g. *FKBP5, ADORA3* (both widely published as GC target genes). When intersecting our complete list of GC regulated genes in macrophages with the list of differential genes identified during preterm labor by Paquette *et al.* we find that 16/39 (41%) of the "preterm labor genes" are GC responder genes. These genes -- ADAMTS2, CXCL2, FKBP5, GPR84, GRB10, IL1R2, MERTK, MS4A4A, PER1, PTX3, S100A8, SH3PXD2B, TNFAIP3, TPST1, VSIG4 and ZBTB16 – therefore are likely induced by glucocorticoid pretreatment and not by preterm labor.

Taken together, for the identification of genes associated with preterm labor it is essential to exclude the immediate and the delayed effects of glucocorticoid treatment.

References

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