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Abstract

Introduction Successful pregnancy requires immune tolerance and controlled inflammation at the maternal–fetal interface. The Tyro3–Axl–Mertk (TAM) receptor tyrosine kinases and their ligands Gas6 and Protein S modulate immune homeostasis. Their temporal roles in uterine regulation during implantation and decidualization remain unclear. We hypothesized that TAM signaling is essential for establishing uterine tolerance and tissue remodeling.

Methods Uterine tissues were collected from mice in estrus and on gestational days 1, 4, 5, 8, 15, and 21. Warfarin was used to pharmacologically inhibit TAM activation. Immunohistochemistry, Western blotting, RT-qPCR, and ELISA were performed to assess expression and cytokine profiles. Immunoprecipitation was conducted once due to limited phospho-specific antibody availability, but the phosphorylation results obtained were clear and interpretable.

Results AXL expression peaked at days 4–5 and localized to the primary decidual zone, whereas MERTK and PROS1 increased later (days 8–15). GAS6 was abundant at D0–D4 but decreased after D5. TYRO3 shifted from luminal epithelium to decidual and embryonic regions. Warfarin inhibited phosphorylation of all TAM receptors, restricted their expression to epithelial layers, and suppressed GAS6 and PROS1 signals. Cytokine imbalance followed (↑IL-10, TNF- α , IFN- γ). Notably, TAM inhibition on day 5 completely prevented decidualization, confirming its necessity for uterine remodeling.

Conclusion TAM receptor signaling dynamically regulates uterine immune tolerance and tissue remodeling. Inhibition at the implantation window disrupts cytokine equilibrium and blocks decidualization, suggesting that the Tyro3–Axl–Mertk axis is indispensable for establishing the tolerogenic environment required for successful pregnancy.

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