# TGF-B1 TRANSACTIVATES ADAMTS-2 (ADAM METALLOPEPTIDASE WITH THROMBOSPONDIN TYPE 1 MOTIF 2) IN SAOS-2 CELLS THROUGH CANONICAL AND NON-CANONICAL PATHWAYS

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*Osteosarcoma is a malignant bone tumor that is common in children and adolescents. The tumor microenvironment is highly effective in the development and progression of osteosarcoma. Transforming growth factor-β (TGF-β) is one of the most abundant cytokines in the tumor microenvironment, and can regulate tumor initiation, progression, and metastasis promoting extracellular matrix (ECM) remodeling and epithelial-mesenchymal transition (EMT). ADAMTS (ADAM Metallopeptidase With Thrombospondin Motifs) proteases have critical functions in normal and tumor microenvironments by processing individual proteins in the ECM. ADAMTSs contribute to tissue remodeling, inflammation, cell migration and, angiogenesis. Among the family members, ADAMTS-2 is a well-known example for ECM remodeling which cleaves the N-terminal propeptide of procollagen and promotes correct collagen fibrillogenesis. Cytokines can regulate normal and tumor microenvironments by affecting ECM proteins. In this study, the effect of TGF-β1, on the transcriptional regulation of the ADAMTS-2, which is an essential enzyme for ECM remodeling was investigated in Saos-2 cells. TGF-β1 upregulated ADAMTS-2 expression both at mRNA and protein levels. Transient transfection assays revealed that TGF-β1 was also induced ADAMTS-2 promoter activity. According to the pathway inhibition studies, both canonical and non-canonical signaling pathways and post-translational mechanisms were responsible for the induction. These studies will contribute to future research on ADAMTS-2 mediated ECM remodeling in osteosarcoma.*

***Key words:*** *ADAMTS-2, TGF-β1, Osteosarcoma, Saos-2, Transcriptional Regulation.*

## TGF-B1 ТРАНСАКТИВУЄ ADAMTS-2 (ADAM-МЕТАЛОПЕПТИДАЗУ З ТРОМБОСПОНДИНОМ ТИПУ 1 МОТИВ 2) В КЛІТИНАХ SAOS-2 ТРАДИЦІЙНИМИ ТА НЕТРАДИЦІЙНИМИ ШЛЯХАМИ



Остеосаркома – це злоякісна пухлина, що вражає кістки і є поширеною серед дітей та дорослих. Мікросередовище пухлини є високоефективним для розвитку і прогресування остеосаркоми. Трансформуючий фактор росту-β (TGF-β) – один із найпоширеніших цитокінів у мікросередовищі пухлини; він може також регулювати ініціацію й прогресію пухлини, а також метастази, сприяючи перебудові позаклітинної матриці (ECM) та епітеліально-мезенхімальному переходу (EMT). Протеази ADAMTS (ADAM-металопептидази з тромбоспондиновими мотивами) виконують надзвичайно важливі функції у нормальному та пухлинному мікросередовищах шляхом обробки окремих білків у ECM. ADAMTS сприяють перебудові тканин, запаленню, міграції клітин та ангіогенезу. Серед членів сімейства ADAMTS-2 – це добре відомий приклад перебудови ECM, який розщеплює N-кінцевий пропептид проколагену і сприяє правильному фібрилогенезу колагену. Цитокіни можуть регулювати нормальне і пухлинне мікросередовища шляхом здійснення впливу на білки ECM. У цьому дослідженні вивчали вплив TGF-β1 на транскрипційну регуляцію ADAMTS-2, яка є основним ферментом для перебудови ECM у клітинах Saos-2. TGF-β1 позитивно регулював експресію ADAMTS-2 на рівні мРНК і білку. Аналізи тимчасової трансфекції також показали, що TGF-β1 індукував промотерну активність ADAMTS-2. Згідно з дослідженнями інгібування шляхів, за індукцію відповідають і традиційні, і нетрадиційні сигнальні шляхи й пост-трансляційні механізми. Ці дослідження будуть корисними для майбутніх досліджень щодо ADAMTS-2-опосередкованої перебудови ECM в остеосаркомі.

***Ключові слова:*** ADAMTS-2, TGF-β1, остеосаркома, Saos-2, транскрипційна регуляція.

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