Identifying the Role of TEAD Proteins and the Pharmacological Disruption of YAP1 to Inhibit the Function of Oncogenic YAP1 Fusions

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Gene fusions are chromosomal aberrations thought to have oncogenic functions, causing nearly 20% of global cancer morbidity rates. This investigation focused on YAP1 fusions. YAP1 (yes associated protein 1), a proto-oncogene driving cell growth, functions via interaction with TEAD (Transcriptional enhancer factor) proteins. This project aims to identify the role of the four TEAD proteins on YAP1 activity of YAP1-MAMLD1 (in brain tumors) and YAP1-TFE3 (in soft tissue sarcoma), and the ability of Dasatinib (nuclear exclusion triggering drug) to inhibit YAP1 activity in the fusions. Firstly, presence of all four TEAD proteins was determined using a polymerase chain reaction. Next, RNA interference was used to silence specific TEAD proteins, then a luciferase assay (that measures gene activity using light) was used to measure YAP1 activity. Finally, after seeding cells with different concentrations of Dasatinib, another luciferase assay was used to measure YAP1 activity. The presence of all 4 TEAD proteins in the cell line were confirmed. TEAD 2 and 4 were expressed at significantly higher levels than TEAD 1 and 3 ($padj < 0.002$). Furthermore, wild type YAP1 ($padj = 0.0004$) and YAP1-MAMLD1 ($padj < 0.0001$) showed significant reduction in YAP1 activity upon silencing of TEAD1-4 expression, while it seemingly had no significant effect on YAP1-TFE3. Lastly, Dasatinib treatment led to significant reduction of wild type YAP1 activity ($p = 0.002$). These indicate that YAP1 activity in the fusions relies on TEAD interaction, hence the YAP1/TEAD complex has high potential as a therapeutic target to stop cancer proliferation.

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