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Transglutaminase (TG2) is a direct target of YAP-TAZ–Reply

Matthew L. Fisher[1], **Gautam Adhikary**[1], **Candace Kerr**[1], **Daniel Grun**[1], and **Richard L. Eckert**[1,2,3,4]

[1]Department of Biochemistry and Molecular Biology, University of Maryland School of Medicine, Baltimore, Maryland, 21201

[2]Department of Dermatology, University of Maryland School of Medicine, Baltimore, Maryland, 21201

[3]Department of Reproductive Biology, University of Maryland School of Medicine, Baltimore, Maryland, 21201

[4]Marlene and Stewart Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, Baltimore, Maryland, 21201

Transglutaminase 2 (TG2) is an important cancer stem cell survival protein (1–4). Our recent manuscript described a novel transglutaminase 2 (TG2) signaling pathway whereby TG2 enhances cancer stem cell survival, spheroid formation, matrigel invasion and tumor formation in squamous cell carcinoma (5). We showed that TG2 triggers these events by activating an integrin, FAK, Src, PI3K signaling cascade that phosphorylates PDK1 causing it to dissociate from LATS1 to inhibit LATS1 activity. Inactivation of LATS1 leads to accumulation of non-phosphorylated YAP1 which then interacts with and stabilizes ΔNp63α which drives the cancer stem cell phenotype (5). Dr. Hong and colleagues, in a letter to the editor, noted that our paper did not describe regulation of TG2 by YAP1 in SCC-13 and HaCaT epidermis-derived cancer cells (5). In particular we did not observe a change in TG2 level in squamous cell carcinoma cells expressing YAP(S127A), a constitutively active form of YAP1, or in cells treated with YAP1-siRNA. This is in contrast to their observation that YAP1 and TAZ interact with the TG2 promoter to regulate TG2 mRNA and protein level in MCF10A, HaCaT and HCT116 cells (6). Although we have not studied the impact of YAP1 or TAZ on TG2 gene expression, we can confirm that TG2 is regulated by YAP1 and TAZ in some cell lines. For example, Fig. 1 shows a reduction in TG2 level in MCF-7 cells following treatment with YAP1 or TAZ- specific siRNA, and confirms that this is associated with reduced spheroid formation. Thus, we conclude based on these findings that TG2 can be regulated by YAP1 and TAZ, but we further propose that this may depend upon the cell type and the cellular environment.

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Conflict of Interest: The authors declare no conflict of interest.

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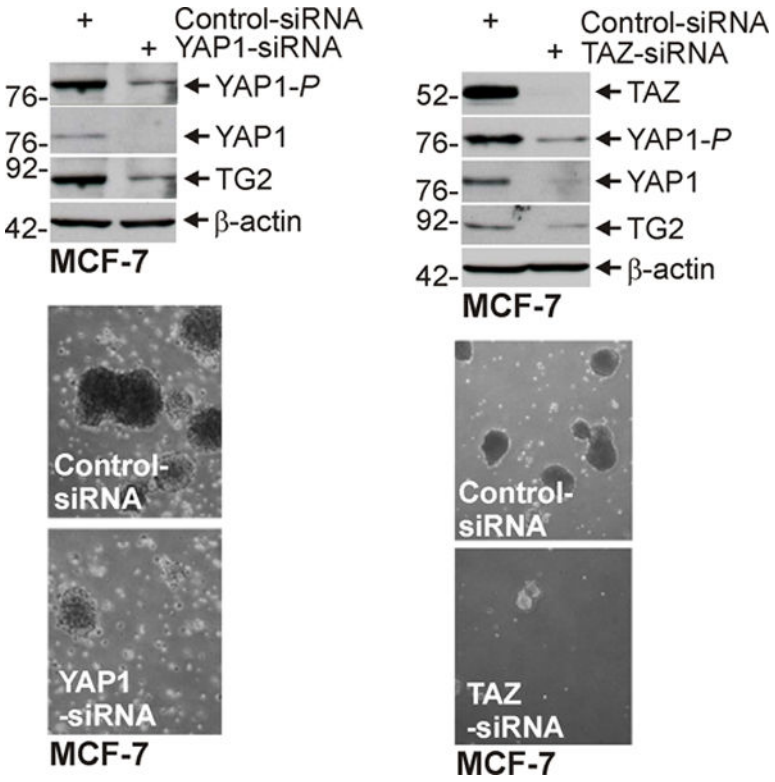

Fig. 1. YAP1 and TAZ control of TG2 level in breast cancer stem cells

MCF-7 cells were double electroporated with Control-, YAP1- or TAZ-siRNA and after 48 h extracts were prepared to monitor the level of the indicated proteins and the extent of spheroid formation as previously described. These studies show that YAP1 knockdown reduces TG2 level, and that TAZ knockdown reduces YAP1, YAP1-*P* and TG2 level. We performed parallel experiments and showed that YAP1- or TAZ- knockdown reduces MCF-7 cell spheroid formation. Similar results were observed in each of three separate experiments.