Cell type-specific YAP1-WWTR1/TAZ transcriptional responses after autophagy perturbations are determined by levels of α-catenins (CTNNA1 and CTNNA3)

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\textbf{ABSTRACT}

The YAP1-WWTR1/TAZ transcription co-factors are key determinants of cell growth that are perturbed in many cancers. Previous studies have reported divergent responses in YAP1-WWTR1/TAZ activities after autophagy perturbations in different contexts. Recently, we identified that α-catenin levels determine whether YAP1-WWTR1/TAZ signaling will be increased or decreased after macro-autophagy/autophagy inhibition/induction. CTNNA1/α-catenin can act as a switch in this pathway, as it is an autophagy substrate and a negative regulator of YAP1-WWTR1/TAZ. However, YAP1-WWTR1/TAZ are also directly degraded by autophagy and there is a feedback loop where YAP1-WWTR1/TAZ positively regulate autophagy. These features were integrated into a mathematical numerical model based on a set of differential equations in order to clarify the integrated output on YAP1-WWTR1/TAZ activity at different time-points after autophagy perturbation in cells with distinct initial levels of α-catenins (CTNNA1 and CTNNA3). Our theoretical and experimental data allow an understanding of cell-type specific and time-dependent responses to autophagy manipulations that may be relevant in many contexts, including different types of cancer.

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autophagy-YAP1-WWTR1/TAZ-autophagy feedback loop, with the initial levels of α-catenin as a key variable explaining the output differences in YAP activity among various cell types.

As most of the perturbations (external or internal) that impact the autophagy pathway induce gradual, and not instant changes, the autophagy-YAP1-WWTR1/TAZ system is dynamic and integrates, at any time point, the three mechanisms mentioned above: (i) autophagy directly degrades YAP1-WWTR1/TAZ, (ii) autophagy indirectly (by suppressing α-catenins) stimulates YAP1-WWTR1/TAZ, and (iii) YAP1-WWTR1/TAZ boost autophagy (Figure 1). Consequently, we also expected distinct output effects on YAP1-WWTR1/TAZ activities at various times after triggering the autophagy perturbation in certain cell types.

To explore this postulated time-dependency of the autophagy-YAP1-WWTR1/TAZ loop after autophagy perturbation, we developed a numerical mathematical model based on three coupled differential equations that follow the temporal evolution of the three inter-linked variables: autophagy, YAP activity, and levels of α-catenins. As this is a dynamic process, the values of the variables at a given time-point depend on previous steps, while the evolution rates of our variables depend on their values at a given time-point. Our mathematical simulations enabled us to decipher the differences in the temporal evolution of YAP1-WWTR1/TAZ activity when we explored scenarios

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**Figure 1.** Autophagy-YAP1-WWTR1/TAZ-autophagy loop. (A) The three mechanisms that control the autophagy-YAP system: (left, in green) autophagy indirectly (by suppressing α-catenin via LIR-dependent degradation) stimulates YAP1-WWTR1/TAZ activity; (right, in red) autophagy directly represses YAP1-WWTR1/TAZ (autophagy directly targets YAP1-WWTR1/TAZ for degradation); (middle, in gray) the feedback generated by YAP1-WWTR1/TAZ activity boosting autophagy. (B) Mathematical modeling for cells with high α-catenin (CTNNA1 and CTNNA3) onset levels: the indirect effect of autophagy inhibition on YAP1-WWTR1/TAZ activity (green) overcomes the direct effect (red) for the entire duration of autophagy perturbation. (C) Mathematical modeling for cells with low α-catenin onset levels: the indirect effect of autophagy on YAP1-WWTR1/TAZ activity (green) is initially dominated by the direct effect (red), but the balance is reversed over time after autophagy inhibition. \( Y_i \) represents the initial YAP activity, and \( t \) represents time.
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Disclosure statement
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