Do drugs that target mTOR generate CCN2-mediated fibrogenic side effects?

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Received: 20 April 2019 / Accepted: 30 April 2019 / Published online: 22 May 2019
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Abstract

mTOR, the target of rapamycin, has been promoted as a potential target for cancers, transplantations and even lung fibrosis. However, paradoxically, targeting mTOR has been reported to result in profibrotic side effects. Some recent publications highlight why this might be.

Keywords CCN2 · CCN3 · CCN1 · mTOR · Rapamycin · Everolimus · Fibrosis

One of the reported side-effects of drugs targeting mTOR is the development of fibrosis. For example, the pro-fibrotic effects of the mTOR inhibitor evrolimus, a rapamycin derivative that is an allosteric mTORC1 (mammalian target of rapamycin complex 1) inhibitor, have been confirmed in vivo in transplant patients using an arbitrary score of pulmonary fibrosis in patients treated with evrolimus. Specifically, an increased level of evrolimus in blood was positively correlated with the extent of pulmonary fibrosis (Tomei et al. 2016). Moreover, in another study, patients using evrolimus showed an increased progression of pulmonary fibrosis (Malouf et al. 2011).

Recently Granata and colleagues (2018) published that evrolimus increased the expression of markers of epithelial mesenchymal transition in primary bronchial epithelial cells; indeed, a cohort of ~125 genes involved with extracellular matrix synthesis was induced. Perhaps not surprisingly, CCN2 was detected as one the genes most induced in response to evrolimus. The authors found that evrolimus also upregulated CCN2 in hepatic stellate cells.

These data are especially useful in light of a recent study indicating that fibrogenic effects downstream of TGFβ in primary lung fibroblasts are mediated by mTOR/4eBP1 (Woodcock et al. 2019). The principal

readout of this latter study was collagen production. Specifically, ATP-competitive mTOR inhibition with AZD8055 and CZ415 inhibited TGF-β₁-induced collagen synthesis, in a concentration-dependent manner, in both healthy and fibrotic lung fibroblasts. Intriguingly, the effect of the partial allosteric mTORC1 inhibitor, rapamycin, was also tested. In contrast to the ATP-competitive mTOR inhibitors, which directly bind to the mTOR catalytic site, rapamycin had no effect on TGF-β₁-induced collagen synthesis. Of particular interest, however, CCN1 and CCN2 levels were enhanced, whereas CCN3 levels were suppressed, by both classes of mTOR inhibitors. These data are important due to the purported role of CCN2 as an essential mediator of fibrosis, including in the lung.

Collectively, these data suggest that, to predict possible long-term clinical outcome, clinical investigation of mTOR inhibitors (eg omipaslsib) (Lukey et al. 2019) should take into consideration whether the levels of CCN proteins are elevated in response to treatment.

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