Toll-like receptor 2: therapeutic target for gastric carcinogenesis

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Gastric cancer is the second most lethal cancer world-wide, and has a poor overall 5-year survival rate of <25% which is largely due to both late detection of this aggressive disease and the limited effectiveness of current treatment options. Surgery alone can only “cure” a small proportion of patients with locally-invasive advanced gastric cancer, and while adjuvant perioperative chemotherapy (e.g. epirubicin, cisplatin, fluorouracil) reduces tumour sizes and improve the 5-year survival rate [1], patient outcomes are largely marginal and often associated with tumour re-occurrence. Moreover, the need for early detection (i.e. screening) and treatment strategies to improve patient survival rates is highlighted by the disappointing results of phase II/III clinical trials worldwide aimed at investigating the safety and efficacy of new drugs for advanced local (resectable) or metastatic gastric cancer.

A recent study by Tye and colleagues has paved the way for new insights into this issue, based on the discovery that the specific and augmented expression of the TLR2 gene in tumours of advanced gastric cancer patients is associated with poor overall survival [5]. Furthermore, genetic and antibody-mediated therapeutic (OPN301, developed by Opsona Therapeutics), targeting of TLR2 in a pre-clinical gastric cancer mouse model displaying elevated gastric TLR2 expression levels dramatically suppressed gastric tumour growth independent of inflammation, thus uncovering a novel growth regulatory role for TLR2 on the gastric epithelium [5].
mutation or gene amplification) that might cause hyper-activation of TLR2, analogous to the epidermal growth factor receptor in lung cancer.

In addition to its newfound role in gastric cancer, TLR2 has been implicated in numerous other inflammatory diseases and cancers, such as lung and pancreatic cancer, arthritis, and ischemia reperfusion (I/R) injury, which collectively make TLR2 an attractive therapeutic target. In this regard, the murine monoclonal antibody OPN301 used by Tye and colleagues to effectively suppress gastric tumour growth is also efficacious in pre-clinical models of kidney transplantation, cardiac I/R injury and pancreatic cancer [6]. Based on these observations, a humanised version of this antibody (OPN305, Opsona Therapeutics) is in late stage clinical development, and will enter a Phase II clinical study in early 2013 to evaluate its safety, tolerability and efficacy in renal transplant patients at high risk of Delayed Graft Function, as the first clinical target indication for OPN305.

We do note, however, the existence of additional approaches to inhibit TLR2 activity in vitro, including short interfering RNA (siRNA), small molecule inhibitors identified in cell based screening assays, and peptide mimetics that prevent ligand-induced receptor signalling of the intracellular domain of TLR2. While the anti-tumour efficacy of such strategies in vivo remains to be explored, a recent in vivo study successfully used TLR2-specific siRNA to block tumourigenesis in a xenograft model of liver cancer [7].

Our recent study suggests that at least in the context of gastric cancer, TLR2 antagonists can ameliorate tumour growth by acting directly on the tumour cells to promote apoptosis and suppress proliferation [5]. However, it is important to consider that TLR agonists (including those for TLR2) can induce adaptive immune responses against cancer cells, which supports the application of TLR agonists in cancer vaccine therapy [8]. Therefore, whether TLR2 antagonists will serve as efficacious therapies against other tumour types, especially those where TLR2 may transmit an anti-tumour immune response will require stringent evaluation in pre-clinical animal-based cancer models.

REFERENCES