SIGNALLING

New roles for TLR2

> indicating that the inflammatory reaction in gastric tumorigenesis was unaffected by *Tlr2* ablation

Gastric cancers are often associated with inflammation. As a result, the activation of Toll-like receptors (TLRs) has been implicated in the pathogenesis of these types of cancer. So, Brendan Jenkins and colleagues investigated this connection further.

The gp130$^{F/F}$ knock-in mouse model spontaneously develops intestinal-type gastric tumours at 6 weeks of age that are driven by interleukin-11 (IL-11)–signal transducer and activator of transcription 3 (STAT3) signalling. Gene expression profiling of tumours from these mice revealed that *Tlr2* mRNA levels were significantly increased and that this was dependent on IL-11 signalling and STAT3 activation. Hyperactivated STAT3, upregulated IL-11 signalling and increased TLR2 expression were also observed in a second transgenic mouse model of gastric cancer and in samples of human gastric cancer, indicating that these factors are important in gastric tumorigenesis. Furthermore, patients with STAT3^{hi} TLR2^{hi} gastric tumours had reduced overall survival in comparison to those with STAT3^{low}TLR2^{low} tumours.

NPG/Neil Smith

What is the connection between STAT3 and TLR2? Chromatin immunoprecipitation experiments showed that IL-11-treated gastric epithelial cells or tumour tissue from gp130$^{F/F}$ mice had phosphorylated STAT3 bound to the *Tlr2* promoter, and further experiments showed that *TLR2* is a target gene of STAT3. Next, the authors investigated whether TLR2 has a role in gastric tumorigenesis. They found that the incidence and mass of gastric tumours were significantly reduced in gp130$^{F/F}$ *Tlr2*$^{-/-}$ mice even though STAT3 activation and IL-11 expression were both upregulated at comparable levels to those in gp130$^{F/F}$ tumours. Surprisingly, histological and immunohistochemical analyses of gp130$^{F/F}$ *Tlr2*$^{-/-}$ tumours revealed that immune cell infiltrates were comparable to those of gp130$^{F/F}$ tumours, indicating that the inflammatory reaction in gastric tumorigenesis was unaffected by *Tlr2* ablation.

If TLR2 is not driving immune cell infiltration of gastric tumours, what is it doing? The gastric epithelium of gp130$^{F/F}$ *Tlr2*$^{-/-}$ mice had a reduced proliferation zone compared with that of gp130$^{F/F}$ mice, and the gp130$^{F/F}$ *Tlr2*$^{-/-}$ surface epithelium was proliferating cell nuclear antigen (PCNA)-negative and had markers of apoptosis, whereas gp130$^{F/F}$ surface epithelium did not. Furthermore, human gastric cancer cell lines treated with TLR2 ligands increased their proliferation in a dose-dependent manner. This proliferation was abrogated by treating these cells with inhibitors of the PI3K–AKT, ERK, JUN N-terminal kinase (JNK) or nuclear factor-κB (NF-κB) signalling pathways, which are activated by TLR2. Consistently, treating gp130$^{F/F}$ mice with a MAPK/ERK kinase (MEK) inhibitor, U0126, suppressed the expression of genes associated with survival, proliferation and the suppression of apoptosis that were induced following TLR2 activation. Finally, treating gp130$^{F/F}$ mice bearing established gastric tumours (at 12 weeks of age) with a TLR2-blocking antibody, OPN-301, twice weekly for 10 weeks substantially reduced the size, number and overall burden of gastric tumours.

Tye *et al.* have characterized a non-inflammatory role of TLR2 signalling in gastric epithelia that promotes survival and proliferation and suppresses apoptosis; therefore, targeting TLR2 could be an avenue for treating STAT3^{hi}IL-11^{hi} gastric tumours.

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