1 | HYPOXIA-INDUCIBLE TRANSGELIN 2 SELECTS EPITHELIAL-TO-MESENCHYMAL TRANSITION AND γ-RADIATION-RESISTANT SUBTYPES BY FOCAL ADHESION KINASE-ASSOCIATED INSULIN-LIKE GROWTH FACTOR 1 RECEPTOR ACTIVATION IN NON-SMALL-CELL LUNG CANCER CELLS

Epithelial-to-mesenchymal transition (EMT) is a process involved in many normal functions, like tissue repair, but it has also been associated with cancer metastasis and γ-radiation resistance. Microenvironmental conditions like hypoxia, through hypoxia inducible factor 1 (HIF-1α), have been shown to induce pathological EMT, but there is a lack of data on other factors in this pathway. In this study, Kim et al examined transgelin 2 (TAGLN2), an actin-binding protein, in non-small-cell lung cancer cell lines. The researchers showed that hypoxia induces TAGLN2 overexpression and causes histologic changes consistent with EMT even in the setting of HIF-1α suppression. Immunoprecipitation showed that these changes were caused by direct interaction between TAGLN2 and focal adhesion kinase, leading to the inhibition of insulin-like growth factor 1 receptor β activation. The data also showed that overexpression of TAGLN2 led to diminished cell death in NSCLC cell lines when exposed to cytotoxic agents. This research provides insight into the underlying biology of tumor recurrence and resistance. https://doi.org/10.1111/cas.13791

2 | BPR1J373, A NOVEL MULTITARGETED KINASE INHIBITOR, EFFECTIVELY SUPPRESSES THE GROWTH OF GASTROINTESTINAL STROMAL TUMOR

The prognosis of patients with nonresectable gastrointestinal stromal tumors (GIST) has improved significantly since the introduction of multitargeted kinase inhibitors (TKIs) like imatinib. However, multiple studies have shown that imatinib resistance is inevitable. Alternative TKIs like sunitinib and regorafenib have only limited improvement against acquired imatinib resistant mutations. In this study, Tsai et al explores the potential therapeutic value of BPR1J373, a TKI with widespread inhibitory activity. They show that BPR1J373 has apoptotic and nonapoptotic mechanisms that inhibit the proliferation of KIT-mutant GIST cells. More importantly, the group showed that BPR1J373 had the most potent suppression of KIT activation in the four most common GIST double mutations. BPR1J373 was also shown to have a noninferior suppression of tumor growth of GIST430 cells when compared to sunitinib in vivo. BPR1J373 deserves further investigation for clinical applications in the treatment of GIST. https://doi.org/10.1111/cas.13773
The immune system has an important role in the suppression of tumor development. There are a variety of mechanisms that cancer exploits to evade the immune system. In this study, Kanemura et al. examined milk fat globule-epidermal growth factor factor 8 (MPG-E8) expression in surgical samples of patients with esophageal squamous cell carcinoma. MPG-E8 has been shown to propagate regulatory T cells and thus suppress the antitumor immune response in mouse models. Here, the researchers show patients with elevated MPG-E8 expression had significantly worse relapse-free survival and overall survival than those with low expression. The rate of high MPG-E8 expression was found to be higher in patients who had received neoadjuvant chemotherapy. These same patients had higher rates of low CD8+ T cell:regulatory T cell ratio and this was associated with worse prognosis. These data produces a potential framework to improve long-term outcomes in esophageal cancer patients treated with neoadjuvant chemotherapy. https://doi.org/10.1111/cas.13785

MALT1 is a paracaspase with a central role in the activation of lymphocytes and other immune cells. In T cells, MALT1 is required for the activation of the transcription factor NF-κB. In this issue, Baens et al. demonstrate that self-cleavage of MALT1 has an important role in regulating NF-κB signaling and immune cell function in vivo. On the one hand, genetic ablation of Malt1 self-cleavage function or its protease activity decreased T cell activation in response to stimulation. On the other hand, MALT1 deficient mice showed a significant reduction in Treg numbers, partly due to a block in IL-2 production. In order to determine which of the two effects would dominate, the authors assessed the anti-tumor immune response in MALT1 deficient mice. Surprisingly, MALT1 deficiency resulted in an increased anti-tumor effect due to increased immune surveillance. Collectively, this study reveals a two-faced role of Malt1 in balancing out the effector and suppressor immune response and its importance in antitumor immunity. Baens M, Stirparo R, Lampi Y, Verbeke D, Vandepoel R, Coops J, Marynen P, Bock CE, Bornschein S, Eur J Immunol 2018, https://doi.org/10.1002/eji.201847597