Our studies of how cytotoxic therapy affects tumor cells have led to a promising translational application in oropharyngeal squamous cell carcinoma (OPSCC), an increasingly prevalent form of head and neck cancer associated with human papillomavirus (HPV) infection.

**Laboratory studies of therapeutic targets in head and neck cancer**

The platinum-based concurrent chemoradiation therapy frequently used to treat head and neck tumors acts in part through the p63/p73 network of proteins. In this network, a form of p63 called deltaNp63 prevents one form of p73 from starting a cellular program that leads to cell death. We found that cisplatin leads to loss of deltaNp63, allowing p73-driven cell death. However, some tumor cells can stay alive after cisplatin treatment if they have high levels of the anti-apoptotic protein Bcl2. We are now studying whether drugs that inhibit Bcl2 function might provide complementary or alternative treatment for tumors whose high Bcl2 levels tend to oppose standard therapy. Our work on Bcl2 and the intrinsic and extrinsic apoptotic pathways has also led us to study the role of caspase 8 in responses of head and neck cancer cells to cisplatin.

**Mechanism-based biomarkers in oropharyngeal tumors**

The incidence of HPV-associated OPSCC, now over 75% of OPSCC cases and accounting for nearly half of OPSCC deaths, has increased 7.5% per year for the past two decades. The high morbidity and frequent failure of chemoradiation therapy for this increasingly prevalent disease indicate the need for improved methods to predict treatment outcome. Extending our basic-science results to the clinic, we found that chemoradiation tends to fail in patients whose tumors have high Bcl2 expression. Notably, we found that Bcl2 and HPV status are not related to each other and provide independent estimates of treatment outcome.
Bcl2 expression and HPV status are both related to outcome in oropharyngeal cancer. Tumor sections from a patient who was cured by concurrent chemoradiation treatment (right) and from a patient who died of disease despite treatment (left), stained with hematoxylin/eosin (H&E) or for human papilloma virus (HPV), the p16 protein (typically high in HPV-positive cases), or the anti-apoptotic protein Bcl2. Overall, Bcl2-high/HPV-negative tumors have poor outcomes, while >90% of patients with Bcl2-low/HPV-positive tumors are cured. Patients with Bcl2-high/HPV-positive or Bcl2-low/HPV-negative tumors have intermediate risk of recurrence. From Nichols et al, Clinical Cancer Research 16: 2138-46, 2010.

Selected Publications:


