The mechanistic role of cellular senescence in development of head and neck cancer

Head and neck cancer (HNC) is the seventh most common cancer worldwide, and accounts for over 800,000 new cases and over 400,000 deaths annually. Tobacco use represents the most significant risk factor for HNC in developing countries, increasing the chances of cancer by 5-25 fold when comparing to non-smokers. Human papillomavirus (HPV) infections represent second significant cause of HNC often affecting younger, non-smoking individuals. HNC is generally treated with surgical resection, followed by adjuvant radiation or chemotherapy plus radiation depending on the disease stage. Cancer of the head and neck can arise in several places, but, if diagnosed early, is usually curable. Yet, due to often first diagnosis at advanced stages, cancer is incurable or requires aggressive treatment significantly affecting quality of life. Thus, better prediction, early diagnosis and prevention provide higher chances for survival. However, to increase the success for early diagnosis and prevention we must first understand the mechanism underlying development and progression of HNC and find out how to decrease the development risk especially in smokers. The link between smoking and cancer is postulated to be mediated by repeatable, chronic insult on squamous cells, thus causing cellular stress and, consequently, enhanced premature cellular senescence (Stress induced premature senescence/SIPS) that is perceived as one of the most critical cancer risk factors. Cellular senescence is a key component of a natural process of human aging that can be induced by a range of stimuli, including DNA damage, cellular stress, telomere shortening, and the activation of oncogenes. Senescence is generally regarded as a tumor suppressive process, both by preventing cancer cell proliferation and suppressing malignant progression from pre-malignant to malignant disease. It may also be a key effector mechanism of many types of anticancer therapies, such as chemotherapy, radiotherapy, and endocrine therapies, both directly and via bioactive molecules released by senescent cells that may stimulate an immune response by release of pro-inflammatory signals. However, despite potential defensive mechanism at early stages, high accumulation of senescent cells may contribute to carcinogenesis as well as reduced patient resilience to cancer therapies and may provide a pathway for disease recurrence after anti-cancer interventions due to weakening immune responses over time through constant chronic inflammation. There are a lot of studies focused on cellular senescence in different diseases including variety of cancer types. But there is a gap in understanding the link between smoking, cellular senescence and HNC – possible association and the mechanism remains unknown.

Based on available literature and our preliminary studies our overarching hypothesis is that tobacco-associated cellular stress increases the level of cellular senescence, and application of senolytic drugs, selectively eliminating senescent cells in smokers will decrease the risk of HNC development due to suppression of the inflammation after chronic tobacco exposure.

To test our hypothesis, we will use a Mouse Cigarette Smoke Oral Cavity and Esophageal Carcinogenesis Mouse Modeled that will provide conditions and results that can be translated into humans.