Tracking down the cells that produce cancers of the tonsil caused by HPV infection

The cells that cover the inside and outside surfaces of many adult tissues are called epithelia. The cells most external to the tissue usually don't survive very long and must be therefore be continuously replaced. This is achieved by the maintenance of a "stem cell population" in the tissue. These stem cells are poised to produce the specialized mature cells characteristic of the tissue and do so when they divide. However, more frequently, they make daughter cells with their same poised features so that their numbers are permanently sustained. These critical cells and their immediate progeny are thought to be the most likely to give rise to cancers since they already possess a capacity to divide many times during which time they can accumulate mutations that cause them to become malignant.

Human Papilloma Virus (HPV) is a well-established cause of cervical cancer, and cancer of the oral cavity is now emerging as an HPV-cancer epidemic. Contrary to a decreasing burden of smoking-related oral cancer where tobacco use has decreased, the incidence of HPV-positive oral cancer – especially in the tonsil and base of tongue – has steadily increased, particularly in many developed countries; indeed, the number of HPV-positive oral cancers in men in the United States has already surpassed that of HPV-positive cervical cancers in women. HPV is thought to cause cancer by insertion of its DNA into the genome of host cells which then deregulates control of the division and differentiation of all of the daughter cells.

Stem cells have been well studied in a number of tissues, but very little was known about the stem cells of the epithelium that covers the tonsil. The present study was therefore designed to characterize the cells of the tonsillar epithelium that have extensive proliferative ability and then to determine how their growth might be altered when they were forced to express the HPV genes thought to have cancer causing effects.

An unusual feature of the tonsil (which is actually a big lymph node) is its possession of deep invaginations of its external surface and a change in the epithelial covering of the so-called "crypts" created by these invaginations. In these crypts, the epithelial cells are not tightly linked together as they are on the outside surface and the cells barely touch each other. Moreover, it had been noted that oral cancers of the tonsil appear to start in these crypts, suggesting that the epithelial stem cells of the crypt might be different in their properties or organization. We were therefore particularly interested in determining whether tonsillar epithelial stem cells are located in one or both sites and what their properties might be.

Our studies show that large numbers of tonsillar epithelial stem cells are located in both sites and have the same unique surface markers that allow them to be selectively enriched and further characterized. More detailed comparisons showed the crypt of the tonsil, in fact, contains a relatively higher proportion of the most primitive epithelial cells.

When we purified these cells and infected them with a non-replicating virus encoding cancer-causing genes derived from HPV16 (the most common type of HPV found in tonsillar cancer), this caused the cells to grow uncontrollably, and created abnormal-looking daughter cells that appeared to mimic what might be the beginning stages of tonsillar cancer.

We expect these findings will now make possible further investigations of how HPV causes oral cancers. It will also provide a test bed for evaluating new biomarkers and factors that enhance the cancer-causing effects of HPV genes, as well as setting the stage for identifying new treatment targets and strategies.

Connie Eaves
Terry Fox Laboratory, British Columbia Cancer Agency
Vancouver, Canada

Publication

Characterization of Epithelial Progenitors in Normal Human Palatine Tonsils and Their HPV16 E6/E7-Induced Perturbation.
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