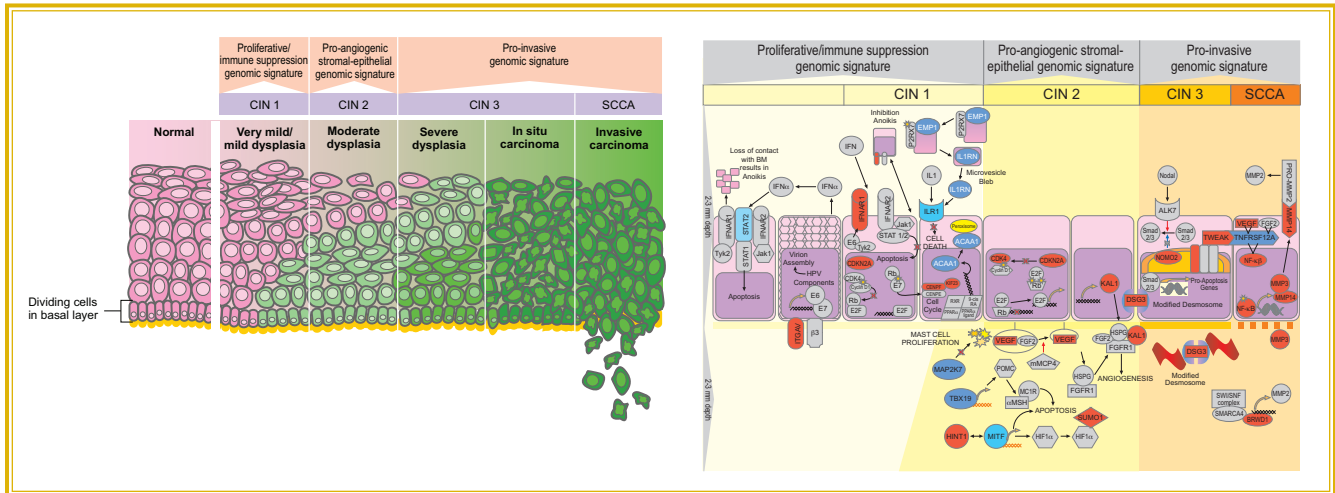


Taking Time-Lapse Genomic Snapshots of Cervical Cancer



(Image: J. Kelly)

Striking shifts in gene expression at different time points in the process of cervical cancer development, from human papillomavirus (HPV) infection to invasive carcinoma, may help reveal how HPV goads cervical cells into becoming cancerous and why the process of carcinogenesis varies so much from woman to woman.

Researchers and physicians have known for over a quarter of a century that human papillomavirus (HPV) infection underlies the vast majority of cervical cancers. While the approval of the first HPV vaccine¹ in 2006 was a breakthrough in cervical cancer prevention, important questions remain. How does the virus fuel cervical cancer development and why do the developmental steps vary from woman to woman?

Not all women who contract HPV develop cervical cancer. In many, the series of precancerous changes triggered by the virus, called cervical intraepithelial neoplasia (CIN), progresses to a certain point and simply stops. In those women who do develop cancer, the process can take mere months or go on for years.

Answering the how and why would be easier if researchers had a time-lapse series of genomic snapshots spanning the cellular progression from viral infection to invasive malignancy. In the August 1, 2007, issue of *Cancer Research*, a multi-institutional team of

scientists including CCR's David Gius, M.D., Ph.D., Head of the Molecular Radiation Oncology Section, unveiled just such a comprehensive photo series. Working with Janet Rader, M.D., and colleagues at Washington University School of Medicine in St. Louis, Mo., Gius examined gene expression within the cervical epithelium (the layer of cells that HPV infects and where cervical cancer originates) and the underlying stroma (normal cells that form a developing tumor's microenvironment) at different histological time points in cervical cancer development.

The team found striking shifts in gene expression that correlated closely with the progressive changes seen under the microscope as the cervical epithelium transforms. Their results suggest three distinct genomic phases in the development of cervical cancer. First, an immunosuppressive phase, characterized by genes linked to the establishment of HPV infection and immune system evasion. Second, a pro-angiogenic phase, where the precancerous cells "talk" to the nearby stroma and encourage the production of factors fostering blood vessel growth, possibly corresponding to the "angiogenic switch" proposed a decade ago by the late Judah Folkman, M.D. Finally, a pro-invasive phase, associated with genes that promote the breakdown and invasion of neighboring healthy tissues.

Together these results constitute an *in vivo* model of cervical cancer development that both provides a window on the evolution of cervical cancer and highlights a number of genes with prognostic and therapeutic potential.

¹See "A Victory against Cancer: 25 Years in the Making," CCR Connections, Vol. 1, No. 1.