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Editorial overview: Viruses and cancer

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It is conservatively estimated that viral infections contribute >10% of all human cancers. In this special section of '*Current Opinion in Virology*', we have asked noted experts in the field to provide their opinions on topics that are timely and relevant in viral oncology, albeit in some cases controversial.

Infections with 'high-risk' human papillomaviruses alone account for 50% of all virus-associated human cancers, in particular cervical carcinomas. A major breakthrough in the prevention of HPV-associated cancers was the development of effective prophylactic vaccines that prevent infections with the most abundant high-risk HPVs. These vaccines have been in use in many countries since 2006. However, since HPV-associated tumors generally arise year or decades after the initial infection, it has been clear since the beginning that it would take years before the impact of these vaccination programs became apparent. In this issue, Silvia de Sanjose, Maria Brotons, D Scott LaMontagne and Laia Bruni have summarized the encouraging results of the currently active vaccination programs. They review the compelling evidence that in countries where vaccination rates have been high, these efforts have caused a measurable decrease in cervical lesions caused by vaccine-type HPVs. Their discussion also provides a roadmap for the future goal of greatly decreasing the number of HPV-associated cancers.

One concern with the vaccination program is that the initial efforts have specifically targeted females. However, it has become clear that HPV infections also cause other tumors, particularly anal and head and neck carcinomas, in both genders. Moreover, in contrast to the decreasing numbers of cervical cancers, the relative fraction of HPV-associated anal and head and neck carcinomas has steadily increased over the recent years. Similar to cervical carcinomas, these cancers arise years to decades after infection, but unlike cervical cancers there are no widespread early detection programs for these tumors. Interestingly, there appear to be some features of HPV-associated anal and head and neck cancers that are not shared by cervical carcinomas. Almost all of HPV-associated anal and head and neck tumors are triggered by infections with one specific high-risk HPV type, HPV16, whereas cervical carcinomas are also caused by several other high-risk HPVs. In addition, HPV-associated head and neck cancers are associated with a different risk factor profile than HPV-negative cases, as they occur in younger individuals who are non-smokers and do not abuse alcohol. An article written by Jitesh B Shewale and Maura L Gillison summarizes these observations and discusses how prophylactic vaccination will likely also have a major impact on this cancer type.

Oncogenesis by HPVs relies on extensive interactions with the cell, and in many cases HPVs target processes that have wide-ranging cellular

consequences. Particularly, there is ample evidence that HPVs deregulate cellular transcriptional programs at least in part via microRNAs, which are small noncoding RNAs that interact with cellular messenger RNAs, causing their degradation or inhibiting their translation. Each microRNA has a multitude of messenger RNA targets that are involved in various cellular signaling pathways. Barbara C Snoek, Iris Babion, Danijela Koppers-Lalic, Dirk M Pegtel and Renske DM Steenbergen review evidence that HPVs subvert the cellular machinery that is involved in the synthesis of microRNAs. The authors also point out that such virus-induced defects in the microRNA processing machinery can give rise to synthesis of abnormally processed microRNAs. These abnormal microRNAs may be of great value as biomarkers for HPV-associated lesions and cancers.

For most tumor viruses, the establishment of a long-term persistent infection ('latency') is a hallmark of carcinogenesis. This persistence necessitates successful long-term inhibition of innate cellular defense mechanisms as well as the ability to undermine recognition and elimination by the adaptive immune system. Vural Yilmaz and Katerina Strati discuss how many human cancer viruses have also evolved the ability to regulate the plasticity of infected cells to convert them into a more 'stem-like' state. In addition, many viral tumors are associated with changes in metabolism that are needed to support viral replication or latency. Micah Luftig and John Purdy discuss current findings on the altered cancer-like metabolism that characterizes many virus infected cells.

A major outstanding question in tumor virology is whether there are additional *bona fide* oncoviruses beside HPVs, gamma-herpesviruses, HTLV-1, Merkel cell polyomavirus and hepatitis B and C viruses. In particular there is an emerging idea that viral infections could in principle contribute to cancer initiation and/or progression without being consistently detectable in every tumor cell ('hit-and-run'). If this is true, viral infections could contribute to a much larger fraction of human tumors than is currently appreciated. One virus that may fit the bill for 'hit-and-run' carcinogenesis is the human BK polyomavirus. Almost all humans are infected with the human BK polyomavirus early in life and the virus remains dormant without overt disease manifestations in immunocompetent individuals. In immunosuppressed individuals, particularly in kidney transplant recipients, BK infections can cause nephropathy. The article by Gabriel J Starrett and Christopher B Buck reviews emerging evidence that BK virus may also contribute to bladder cancer, particularly in transplant patients. In addition to expressing viral genes that can inhibit cellular tumor suppressor pathways, the oncogenic activity of BK may be due in part to activation of the APOBEC3B enzyme. APOBEC3B is a component of a cellular antiviral defense system that is designed to inactivate invading, rapidly proliferating pathogens by mutagenizing their genomes, but also causes mutations in the host cell genome that may facilitate carcinogenesis independent of continued viral gene expression in every tumor cell.

Also in this issue, Charles Cobbs reviews a similarly controversial association between cancer and another ubiquitous virus, human cytomegalovirus (hCMV). Like all human herpesviruses, hCMV can establish life-long latent infections with episodes of lytic replication. Many of the lytic genes have been shown to manipulate cellular processes that have been dubbed 'hallmarks of cancer'. Cobbs reviews several studies that have proposed that hCMV infections may mechanistically contribute to carcinogenesis under conditions where a subset of lytic genes is expressed without triggering the entire lytic program and elimination of the infected cell.

In addition to these specific examples, the rapidly increasing availability of next generation DNA and RNA sequence data sets provides ample opportunity to identify new cancer viruses (such as the Merkel cell polyomavirus by the Chang/Moore lab in 2008) or to collect data that implicate known viruses as potential human cancer agents. The article by Paul G Cantalupo and James M Pipas provides an excellent primer for such efforts and points out best practices to avoid the many potential confounding factors.

Collectively, the articles in this section reiterate and extend the concept that viruses importantly contribute to cancers. In some cases, exemplified by HPV-associated cervical carcinogenesis, viruses are obligatory triggers for almost all cases of a specific tumor, and they remain necessary for tumor maintenance. Deciphering the intricate interplay between the invading pathogen and the host cell continues to provide fascinating insights and potential opportunities for early detection and/or therapeutic approaches. In other situations, like head and neck carcinomas, viral infections only contribute to fraction of all cases, and it is particularly important to determine the differences and similarities between virus and non-virus associated cases. Computational analyses of existing cancer sequencing data will continue to provide potential evidence for viruses contributing to carcinogenesis, particularly cancers that are more prevalent in long-term immunosuppressed patients. These analyses will be also be useful to identify cases in which the links between viral infection and oncogenesis are more complex, for example situations in which viruses may modulate only some aspects of oncogenesis and/or only transiently infect a tissue to mechanistically contribute to carcinogenesis.