Viral etiology in retinoblastoma

In this era of a viral pandemic of COVID-19, the focus has come back on viruses especially with references to their mode of transmission, diseases caused, and long-term consequences. From the well-known "hit and run" viruses, we now are familiar with the strong association of human papilloma virus (HPV) and cervical cancer and nasopharyngeal cancer with the research leading to development of a vaccine. The viruses in general may leave little or no evidence, may remain latent for many years, indirectly cause loss of cell cycle control, but rarely does it replicate in a tumor nor is the entire viral genome retained. Hence, with regard to implicating a viral etiology to any disease, more than the Koch's postulates one tends to lean toward the use the Bradford Hill criteria,[1] which were developed to establish causation between a specific factor—environmental or otherwise—and a disease. The criteria include strength of association, consistency (replication by other laboratories), specificity, temporality (whether exposure preceded disease), biologic dose gradient, plausibility (credible scientific mechanism), coherence with other evidence, experimental evidence, and analogy. While scientists argue if all criteria should be fulfilled, most agree that the temporality is the key feature.

Retinoblastoma can be considered as a great teacher- it provided insights into Knudson's 2 hit hypothesis, was first gene to be cloned, and finally paved way for prescreening evaluation of embryos that resulted in the birth of a successful unaffected fetus. Mutation of RB1, a tumor suppressor gene on chromosome 13, interacts with over 100 cell proteins and regulates cell cycle through binding and inactivation of the transcription factor E2F. Recent evidence also points toward somatic mutations in MYCN can give rise to RB.

However with regards to viral etiology in RB, evidence for association of HPV and Retinoblastoma keeps surfacing, both in favour and against. When the data of transforming proteins of adenovirus, papillomavirus, and the polyomaviruses BK and JC binding to the product of the RB gene was emerging, Howard *et al*.[2] evaluated and negated for the presence of five human DNA in Retinoblastoma tumor viruses. If the argument goes about the techniques used, then Gillison ML[3] used a myriad of tools like genomic DNA sequences by real-time polymerase chain reaction, genetic and epigenetic alterations in all 27 exons of the RB1 gene locus and promoter by exonic copy number detection, sequencing and methylation-specific PCR of the promoter region. Based on all the above, he reported that substantial quantitative evidence indicated that neither HPV nor any other pRB-inactivating human DNA tumor viruses play a role in the development of RB, regardless of RB1 genotype. However other studies report the presence of viral genome and imply a role in its pathogenesis.[4]

Interestingly, the evidence of role of vertical transmission and persistence of HPV in newborns is also variable. While one study reports no persistent infection in infants at 6 months suggesting a temporary inoculation rather than true vertical infection,[5] another study reported the proportion of HPV positivity in multiple sites including the conjunctiva.[6] However, as always happens in science, search for evidence should continue as they have the potential of influencing the treatment protocols in future.

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Access this article online

Quick Response Code:

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1801_21

Cite this article as: Vemuganti GK. Viral etiology in retinoblastoma. Indian J Ophthalmol 2021;69:1990.

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Dr Geeta K Vemuganti joined School of Medical Sciences, University of Hyderabad as a Professor and Founder Dean, after leading Ophthalmic Pathology Laboratory and Sudhakar and Sreekant Ravi Stem Cell Biology Laboratory at the renowned L V Prasad Eye Institute, Hyderabad. Her experience and expertise is in the area of ocular tumors and stem cell biology, where she has contributed to the cutting edge research that led to bench-to-bedside applications. Her current research includes cancer stem cells in retinoblastoma, new animal models, and human lacrimal gland regeneration. She has published widely, authoring more than 200 papers with an H Index of 46. She is also a recipient of several national and international awards including the recent Senior Achievement award by American Academy of Ophthalmology and Fellow, ARVO. Dr Vemuganti has received many prestigious academic as well as research grants from national and international agencies and has guided many doctoral students in both basic and applied research projects.