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DAY 1

Recent advances in translational genomics of NPC

Translational genomics of nasopharyngeal carcinoma

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Nasopharyngeal carcinoma is a unique cancer with strong etiological association with infection of the Epstein-Barr virus (EBV). With particularly high prevalence in Southeast Asia, the involvement of EBV and genetic aberrations contributive to NPC tumorigenesis have remained unclear for decades. With the recent advances in genomic analysis, multiple aspects of cellular-viral co-operation in NPC tumorigenesis were unveiled. Exome and genome sequencing have defined constitutive NF-kB activation caused by either somatic alterations or by overexpression of *LMP1* as a key event driven tumor progression. A similar spectrum of somatic aberrations and viral gene expression undermined innate and adaptive immunity may evade immune surveillance of NPC despite its pro-inflammatory phenotype. Studies also realize that NPC mutational burden, mutational signatures, MAPK/PI3K aberrations, and MHC Class I gene aberrations, are prognostic for patient outcome. Together with the development of new patient-derived EBV-positive NPC models, the genomic discoveries begin to shape the focus of NPC therapy development. Given the challenge of limited molecular targets in NPC genome, more innovative therapeutic approaches have been explored to target EBV genome and viral oncogenes in NPC. Focused preclinical and clinical investigations on these directions may develop the effective targeting strategies to further improve survival of NPC patients.

Linking ribosomal proteins to nasopharyngeal carcinoma: Implications for diagnosis, prognosis and targeted drug therapy.

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Ribosomal proteins are essential components for ribosome biogenesis – a precursory process in cellular protein biosynthesis. Since the 1990s, their roles in other physiological events such as DNA replication, transcription, DNA repair, DNA splicing and modification, and apoptosis have been documented. As such, ribosomal proteins have been linked to congenital disorders and cancers. We have been tracking their association and activities in nasopharyngeal carcinoma (NPC) since 2008, and to date, the aberrant expression of 12 ribosomal protein genes has been implicated in this malignancy. The ribosomal proteins involved comprise 5 from the large ribosomal subunit (eL14, uL14, eL27, eL41 and eL43), and 7 from the small ribosomal subunit (uS4, uS7, eS8, uS19, eS26, eS27 and eS31). Interestingly, a recent study (via in silico strategy) of ours have also identified 4 ribosomal proteins (eS10, eS25, uL10 and uL11) that can interact with Epstein–Barr nuclear antigen 1 (EBNA1) – the only Epstein-Barr Virus (EBV) protein found in all EBV-related malignancies including NPC. By using a combination of experimental molecular-based techniques and bioinformatics approaches that include gene knockdown, two-dimensional gel electrophoresis, and computational molecular docking simulation, we have very recently identified 15 plausible protein partners of eL27 that are involved in NPC oncogenesis. Taking all our findings from more than a decade of studies, herein we review and explain the molecular mechanism(s) underpinning the carcinogenesis of NPC as understood from the perspective of ribosomal proteins. The knowledge of which would have significant implications on diagnosis, prognosis, and targeted drug therapy on the malignancy of the nasopharynx.

The interplay between EBV, tumor cells, and the microenvironment in NPC

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While viruses play critical roles in many human malignancies, the influence of virus infection on the tumor microenvironment (TME) and how this impacts disease progression are poorly characterized. We performed single-cell RNA-seq on ~104,000 cells from 19 EBV+ nasopharyngeal carcinoma (NPC) and 7 nonmalignant nasopharyngeal biopsies. We have defined the complex interplay between tumor cells, virus infection, and the TME at single-cell resolution. An epithelial-immune dual feature of malignant cells was discovered and associated with poor prognosis. Stromal and immune cells in the TME were remodeled by tumor cells and virus infection. EBV gene expression was found to correlate with complement factor expression in malignant cells, which, in turn, mediated T cell modulation and recruitment. We subtyped NPC patients into 5 groups with different prognoses according to their respective TME compositions. Our results provide new insights into the multicellular ecosystem of NPC and offer important clinical implications.