Retrovirology

Invited speaker presentation

Evolution of TRIM antiviral genes in primate genomes

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In the past few years, researchers in virology have revealed a novel arm of intracellular, cell-autonomous immunity that mammalian cells mount against viral infections. The discovery of this class of antiviral defense has typically relied on host cells from different sources having altered abilities to resist infection by a particular virus. For instance,, the TRIM5alpha gene was discovered in a functional screen because it confers resistance to HIV infection in rhesus macaques and other Old World Monkeys (OWM) but not in humans. Since this functional identification approach is predicated on the rare observation of different susceptibilities to viral infection amongst cells (e.g. rhesus versus human), this traditional approach is likely to miss the bulk of such immunity genes. Indeed, the evolutionary histories of TRIM5 suggests its participation in intrinsic immunity is ancient, yet it was discovered due to its incidental activity against relatively young lentiviruses like HIV-1. This indicates that the cellular arsenal of intrinsic immunity genes honed against retroviruses is large and mostly undiscovered. We aim to exploit another feature common to these intrinsic immunity genes: the unique selective pressures they are subject to by virtue of their antagonistic relationship with retroviruses. For instance, any mutation that improves TRIM5alpha's ability to recognize its viral antagonist (the capsid protein) is advantageous to the host genome. However, the viral capsid is also under stringent selective pressures to mutate to avoid interacting with TRIM5alpha. Repeated rounds of mutation in which one party increases binding affinity while the other party decreases affinity can be likened to a molecular 'arms-race'. We believe that a candidate gene identification approach, based on identifying signatures of such 'arms-races' via evolutionary pressures, is likely to be highly informative to characterize host-virus intracellular interactions in general, and identify novel intrinsic immunity genes, in particular. I will discuss our studies of the TRIM multigene family and innovations observed both in terms of sequence evolution as well as gene-fusion that have helped primates battle retroviruses over the course of evolution.