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HIV-1 Pathogenesis Env fusogenicity and coreceptor expression levels determine bystander apoptosis induction

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HIV-1 infections lead to a progressive depletion of CD4 cells culminating in AIDS. The coreceptor usage by HIV varies from CCR5 (R5) tropic early in infection to CXCR4 (X4) tropic in later infections. While the coreceptor switch from R5 to X4 tropic HIV is well associated with progression to AIDS, the role of CCR5 in disease progression especially in patients infected exclusively with R5 isolates throughout the disease remains enigmatic. To better understand the role of CCR5 and R5 tropic HIV envelope in AIDS pathogenesis, we asked whether the levels of CCR5 and/or HIV Env-mediated fusion determine apoptosis of bystander cells. We generated CD4+ T cell lines expressing varying levels of CCR5 on the cell surface, to show that CCR5 expression levels correlate with bystander apoptosis induction. The mechanism of apoptosis involved caspase-3 activation and mitochondrial depolarization and was dependent on gp41 fusion activity as confirmed by fusion restricted gp41 point mutants and use of the fusion inhibitor T20. Interestingly, lower levels of CCR5 were able to support virus replication in the absence of bystander apoptosis. Our findings suggest that R5 HIV-1 mediated bystander apoptosis is dependent on both CCR5 expression levels as well as fusogenic activity of the Env glycoprotein.

Biography

Dr. Himanshu Garg completed a PhD in Immunology from North Carolina State University in 2003 working on Feline Immunodeficiency Virus. He subsequently completed five year Post Doctoral training at the National Cancer Institute focusing on HIV Env glycoprotein and its role in HIV Pathogenesis. He joined Texas Tech University Health Sciences Center as Research Instructor in 2009 and currently holds this position. He has published more than 20 peer reviewed articles in major journals on a variety of topics including HIV pathogenesis, HIV assembly and gene therapy.

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