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**Analysis of a novel cellular anti-viral mechanism involving RNA cleavage**

**Margo Brinton**

**Georgia State University**

Viruses are intracellular pathogens that activate and counteract cell innate immune and cell stress responses via diverse and complex interactions/pathways. Our knowledge of cell anti-flaviviral responses is still incomplete. Members of the genus flavivirus differ in a number of ways from the members of the other two genera of the family Flaviviridae. A number of these viruses such as West Nile virus (WNV), Japanese encephalitis virus, dengue and tick-borne encephalitis virus, are classified as class A, B, or C NIAID priority human pathogens. A unique characteristic of cells infected with a member of the genus flavivirus is the accumulation of a stable 3' UTR fragment of the viral RNA genome. The levels of this fragment were found to be increased in cells infected with an avirulent WNV strain that produced lower titers of virus compared to a virulent virus strain. These data suggest that this may be a novel anti-flavivirus-specific cellular mechanism. Further study of this mechanism will lead to a better understanding of the flavivirus-host interaction at the molecular level which in turn is expected to facilitate the discovery of novel ways of blocking the ability of flaviviruses to cause disease in humans. The cell nuclease responsible for specific cleavage of the flavivirus genome RNA in the 3'UTR has not yet been identified. Experiments were initially proposed to analyze the possible involvement of three cell endonucleases in the generation of the viral 3' fragment. Data obtained for one of these, G3BP, indicates that it is not the endonuclease responsible for the cleavage of the viral RNA. The involvement of two others will be tested during the next period of this project. Our current knowledge about the contribution of virus strain variation in determining the host response is quite limited. Although the two WNV proteins involved in differential G3BP phosphorylation were mapped. The viral protein(s) involved in differentially regulating the level of 3' RNA cleavage still need to be mapped using a series of lineage 1/lineage 2 chimeric viruses as the first step in analyzing the mechanism involved.