Research Highlight: Revealing molecular mechanism behind the effect of Zika Virus infection on neurodevelopment.

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Abstract: During recent years, a member of *Flaviviridae* family named Zika virus emerged as a prominent human pathogen mostly because of its connection with neonatal microcephaly. While the effect of Zika virus infection on pregnant women especially neuronal development of fetus is well proven, the molecular mechanism behind this in cellular level was not understood. In a recent report in Science, Chavali et al. first time revealed the molecular mechanism behind the effect of Zika Virus Infection on neurodevelopment (Chavali *et.al*., 2017).

Keywords: Zika Virus, Neonatal microcephaly, Musashi1, Musashi2, Neuronal development

A recent report published in Science in June 2017 (Chavali *et.al*., 2017) revealed one of the cellular targets of Zika Virus during neuronal development. The key finding of this report article by Chavali *et. al.* is the discovery of the involvement of the RNA binding protein Musashi 1 (MSI1), a translational regulator in stem cells, during Zika Virus infection. In this report, the authors found that MSI1 interacts with Zika genome and favors virus infection leading to cause neonatal microcephaly.

The Musashi family of RNA binding proteins is highly conserved across species. In mammalian neural precursor cells, two members of this family of protein, Musashi 1 (MSI1) and Musashi 2 (MSI2), are strongly co-expressed and both are important translational regulators in stem cells (Imai *et al*., 2001; Donald *et al*., 2016; Sakakibara *et al*., 1996; Sakakibara *et al*. 2001). While MSI1 and MSI2 are generally co-operatively involved in proliferation and maintenance of neural stem cell populations (Sakakibara *et al*., 2012), Chavali *et. al.* reported that MSI1 and MSI2 do not have complete functional redundancy in Zika Virus replication. According to this report, only MSI1 plays a key role in Zika Virus replication, in primary and neural cell lines. If we consider the mechanism behind the role of MSI1 in stem cell proliferation, it is reported that the ability of MSI1 to regulate progenitor cell maintenance is done by the translational regulation of cell cycle regulator protein p21^{WAF-1} which is a cyclin dependent kinase inhibitor. The 3' untranslated region (UTR) of the native p21^{WAF-1} mRNA contains a MSI1 binding site where MSI1 can bind and repress p21^{WAF-1} translation and knockdown of MSI1 causes aberrant expression of p21^{WAF-1} which blocks neural differentiation (Battelli *et al*., 2006). Chavali *et. al.* identified individuals with mutations in MSI1 that cause autosomal recessive primary microcephaly. In this highlighted report, authors showed that binding of Zika Virus genome to MSI1 disrupts the binding of MSI1 to its endogenous targets as they compete for the same binding site and thus adversely affects neural cell development (Figure 1).

Relation between neonatal microcephaly and maternal Zika Virus infection is now quite well established. The highlighted report by Chavali *et. al.* in Science journal has identified for the first time a cellular factor playing a key role in neonatal microcephaly caused by Zika Virus. Although we have still many questions standing to be answered about the in-depth molecular mechanisms by which MSL1 augment Zika virus replication as well about the role of MSL2 in this process, however, the study presented by Chavali et al, hold great significance in our understanding of the virus to generate anti-viral drugs.

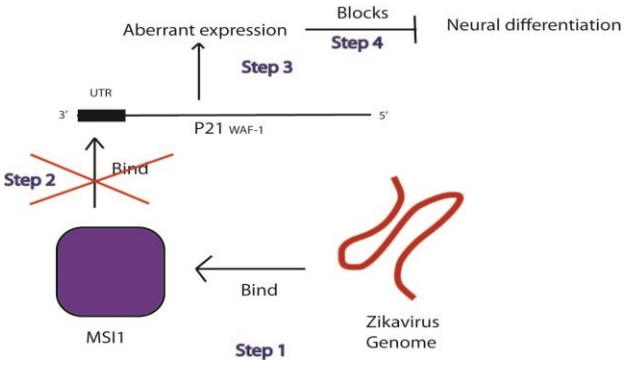

Figure 1

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