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ECS 129 Project #2: Proteins

Part 1 - Visualizing the envelope of a virus

The Zika virus, which is mostly spread by the bite of an infected Aedes mosquito, has become a major global health issue because it has been linked to serious birth problems in newborns of infected mothers, including microcephaly. The possibility of neurological problems and fetal deformities is a concern, even though the majority of Zika infections are asymptomatic or only produce mild flu-like symptoms (Centers for Disease Control and Prevention, n.d.).

A virus's envelope is the lipid bilayer membrane that envelops the viral capsid, which houses the virus' genetic material. When the virus leaves the host cell during the process of viral budding, this envelope is formed from the membrane of the host cell. Because the envelope contains viral glycoproteins that make it easier for the virus to bind to and enter host cells, it is essential to the virus's capacity to infect those cells. These glycoproteins can trigger immunological responses in the host and are frequently targets of the immune system (Medeiros et al., 2023).

The envelope of the Zika virus is crucial for its infectivity and pathogenicity. The envelope glycoprotein, E protein, mediates viral attachment to host cell receptors and membrane fusion during viral entry. Neutralizing antibodies targeting the E protein can prevent Zika virus infection in mice and protect against fetal transmission during pregnancy, highlighting the importance of this vital component in vaccine development and therapeutic strategies (Stettler et al, 2016).

The dimer of the E protein is shown below associated with each of the domains of the protein highlighted in a different color, with Domain I in red, Domain II in yellow, and Domain III in Blue. E protein is the major protein that is involved in receptor binding & fusion of Zika's viral envelope and along with protein M, it is organized in groups of dimers, with 60 total repeating units across the viral surface arranged in icosahedral symmetry. Within protein E, there are 3 domains, Domain III contains the receptor-binding site, contains the fusion loop that interacts with the endosomal membrane during fusion, and DI acts as a bridge between the two. Researchers have also found that while the Zika E protein shows similarities to E proteins in other viruses, it has a more compact surface which may contribute to its higher structural stability and ability to survive in harsh environments like semen, saliva & urine so treatments that

destabilize this structure may help to reduce disease outcomes, like limiting the spread of the virus or it's severity (Kostyuchenko et al 2016).

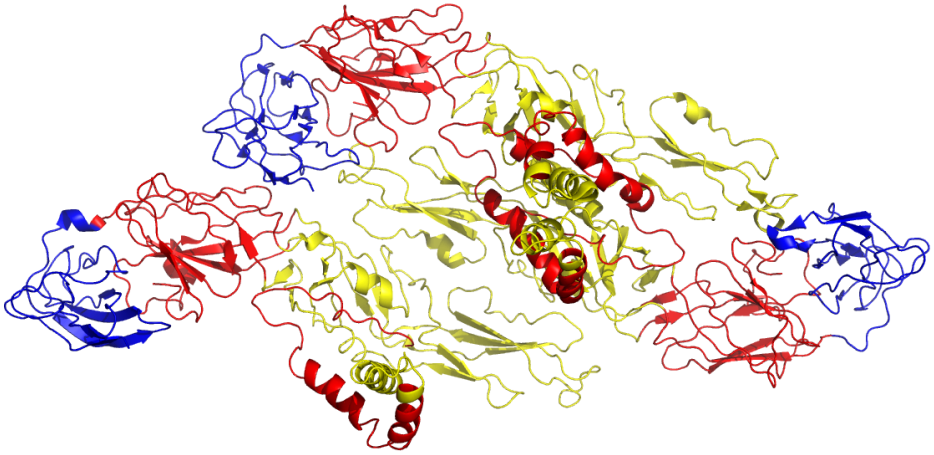


Figure 1: Image of a dimer of the E protein; Domain I is colored red, Domain II is colored yellow and Domain III is colored blue

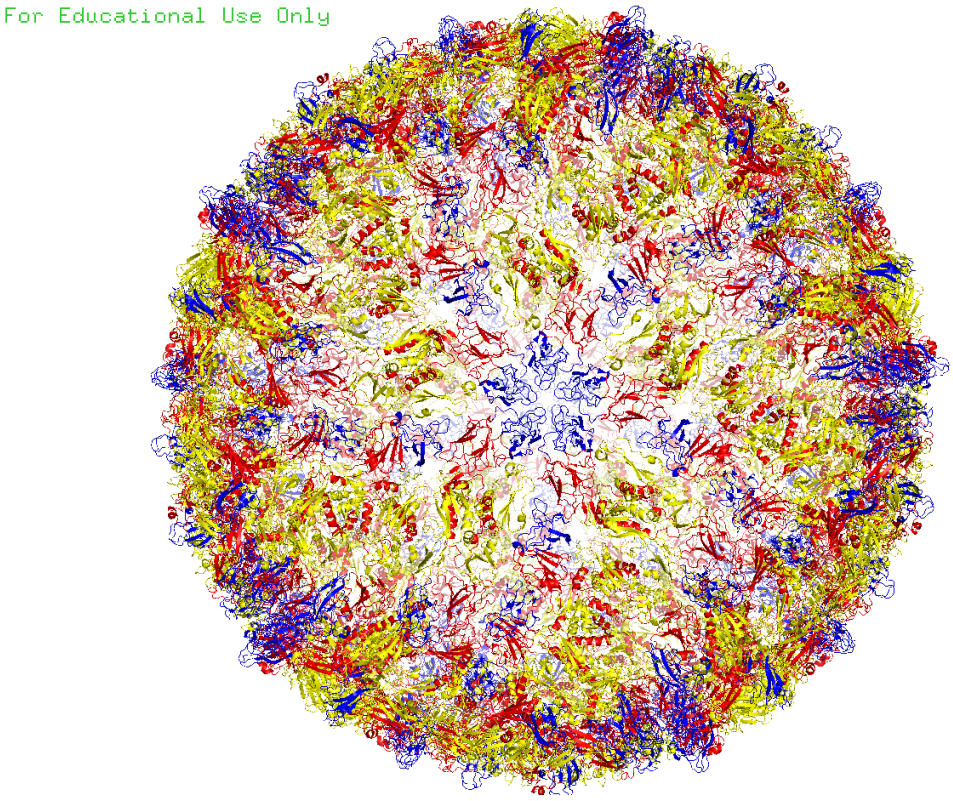


Figure 2: Image of the full envelope of the Zika Virus; Domain I is colored red, Domain II is colored yellow and Domain III is colored blue

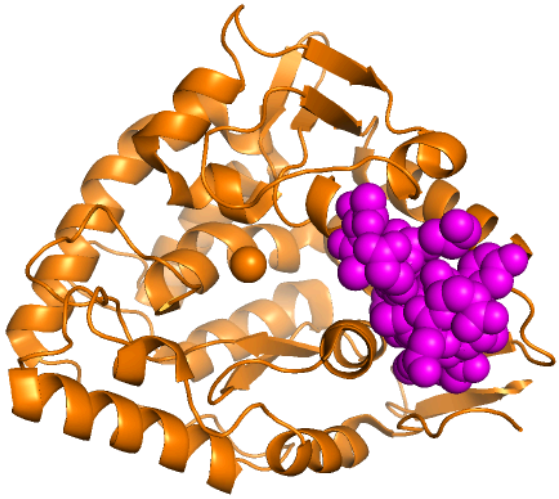
Part 2 – Identification of a Diseases

There is a short fragment of a protein that has been identified as a marker for a human genetic disease. The fragment is GLASLGTPDEYIEKLAT which can be associated with the human gene PAH which codes for the protein Phenylalanine hydroxylase.

To compare the marker fragment with the one-letter code the full wildtype protein must be obtained. The one-letter AA code sequence of the wildtype protein is as follows:

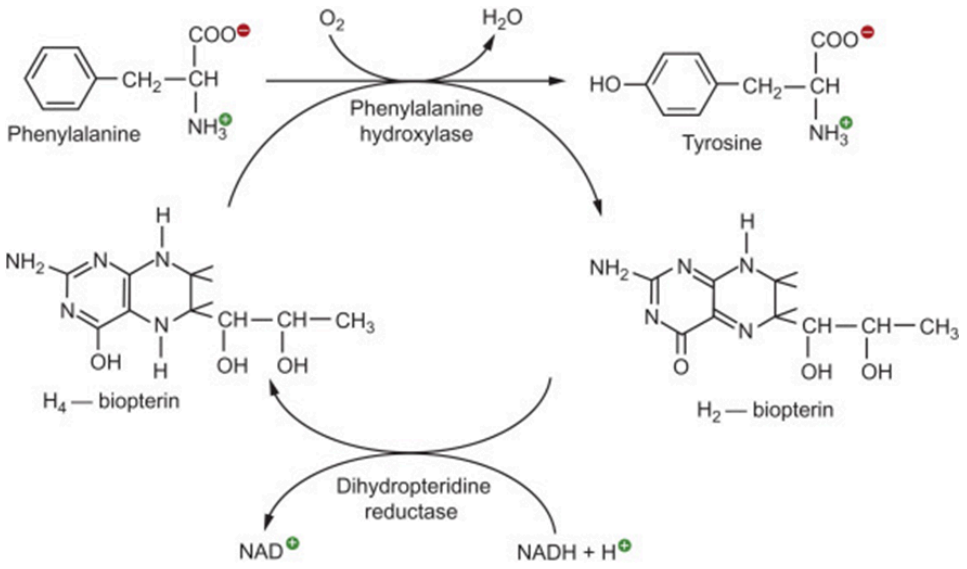
MSTAVLENPGLGRKLSDFGQETSYIEDNCNQNGAISLIFSLKEEVGALAKVLRLFEENDVNLTHIE
SRPSRLKKDEYEFFTHLDKRSLPALTNIIKILRHDIGATVHELSRDKKKDTVPWFPRTIQELDRFAN
QILSYGAELDADHPGFKDPVYRARRKQFADIAYNYRHGQPIPRVEYMEEEKKTWGTVFKTLKSL
YKTHACYEYNHIFPLLEKYCGFHEDNIPQLEDVSQFLQTCTGFRLRPVAGLLSSRDFLGGLAFRVF
HCTQYIRHGSKPMYTPEPDICHELLGHVPLFSDRSFAQFSQEIGLASLGAPDEYIEKLATIYWFTVE
FGLCKQGDSIKAYGAGLLSSFGELQYCLSEKPKLLPLELEKTAIQNYTVTEFQPLYYVAESFNDAK
EKVRNFAATIPRPFSVRYDPYTQRIEVLDNTQQLKILADSINSEIGILCSALQKIK

There is a single mutation present between the marker and the wild-type genome. This happens in the seventh amino acid in the marker fragment or from residue 307-323. Where the wildtype contains an alanine the marker contains a threonine instead. The following is a protein render of the marker



From the model rendered above it can be seen that the protein that is not mutated is colored orange and the marker that contains the mutation is represented as spheres.

The PAH gene provides the instructions for making the phenylalanine hydroxylase enzyme. The enzyme is responsible for the conversion of excess phenylalanine into tyrosine. This chemical reaction is shown below in the diagram



From [Phenylalanine - an overview | ScienceDirect Topics]

Since phenylalanine cannot be produced in the normal human diet it must be ingested. Tyrosine as a result can be produced with the hydroxylation of phenylalanine in the liver. PAH functions as an oxidase as it combines one atom of oxygen into the hydroxyl group that is added to the product and converts the other into water. It also works with a coenzyme tetrahydrobiopterin BH4 which donates two hydrogens in the reaction (ScienceDirect, n.d.).

As a result of this single amino acid mutation the hereditary autosomal recessive disease called phenylketonuria. This disease causes an accumulation of the amino acid phenylalanine in the blood and tissues. The disease results in the decrease or sometimes the elimination of enzyme activity converting the phenylalanine into tyrosine. This poses a threat to a person with PKU as a lot of protein-rich food consumption can lead to serious health problems. The disease causes a lot of symptoms including nervous system problems such as seizures, skin rashes, lighter skin, eyes, and hair because phenylalanine cannot be transformed into melanin, along with a smaller head, intellectual disability, behavioral and delayed development (Sharma et al., 2018). It has also been known to cause organ damage. There are also

different severities as there is classic PKU and less severe forms of PKU. The classic PKU enzyme is completely missing or severely reduced which can cause high levels of brain damage. There are also less severe forms of PKU, in this the enzyme has some function so the phenylalanine levels are not as high however, brain damage is still a threat (Mayo Clinic, 2021). The cause of the disease is the mutation and both the mother and father must have passed the changed gene making it autosomal recessive. Due to the severity of the disease, there are no cures rather it must be managed. One main way is maintaining a proper diet, a low-protein diet must be consumed along with amino acid supplements to ensure proper nutrients. Additionally, food products with aspartame must be avoided as aspartame must be converted into phenylalanine in the body (Mayo Clinic, 2021).

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