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seminar

Wednesday, 26th January, 9.30am, Online

Host: Dr. Ivan Coluzza

Modulating the Conformational Plasticity of Tetraspanin CD81 by Ligand Binders and its Implication in Cellular and Viral Processes

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Hepatitis C virus (HCV) is the second viral agent, after Hepatitis B Virus (HBV), that causes the major number of chronic hepatic infections worldwide. HCV infection comprises several steps since the attachment to the membrane receptors to the delivery of the viral genetic material and replication inside the cells. Tetraspanin CD81 is a key entry factor for HCV as it accompanies the virus during membrane attachment and internalization through clathrin-mediated endocytosis. The HCV-CD81 binding takes place through the $E2_{core}$ glycoprotein.

In this research work we have elucidated the molecular mechanisms that make CD81 and E2 respond to the environmental conditions that take place in the endosomes, in particular, pH. In the case of CD81, these studies have allowed to decipher that pH drives a conformational change (from close to open) in the head subdomain orchestrated by the titration of distal and solvent exposed residues D139 and E188, which are able to regulate the dynamics of the solvent around the entire protein by changing their own interaction with water.

The implications of this conformational change in the function of tetraspanin CD81 in the endosomal pathway are still yet to be clarified, but we hypothesize that the particular response of CD81 to pH is the signal for the protein to exit the endosomal pathway and be recycled to the cellular membrane. In the case of E2, our work has elucidated that pH make the protein more stable, suggesting a possible active role during viral internalization and fusion, and not only receptor engagement.

When these two proteins are studied together, $CD81_{LEL}$ and $E2_{core}$ in complex, their pH response mechanism is completely altered. CD81 does not sense pH anymore with its pH sensors D139 and E188 as their direct interaction with water is screened by the proximal interaction with E2, suggesting that HCV-E2 exploits the pH-sensing mechanism of CD81 to its own purposes. We hypothesize that this pH-sensing blockage serves the virus to keep bound to CD81 in the endosomes until fusion is accomplished. The pH-response of E2 is also altered in presence of CD81. The presence of CD81 induces changes in the pH-sensing of buried and solvent exposed residues in E2 which is translated in an alternating binding mechanism between both proteins. Also, the presence of CD81 primes conformational changes on the E2-CD81 binding loop and we hypothesize that this conformational change on the CD81 binding loop domain is necessary for the further fusion step in the endosomes.

We hope that these findings about the HCV infection process aided by tetraspanin CD81 could help in the design of new antivirals that could block the pH-tuneable binding mechanism between both proteins or their respective pH-dependent conformational changes and so, be used as an alternative for those DAA resistant patients and as prophylactic therapy for high-risk populations.