DIPARTIMENTO DI FARMACIA E BIOTECNOLOGIE

AVVISO DI SEMINARIO

Il giorno giovedì **15 settembre 2022**
alle ore **16.00**

in presenza:

Aula A – Ex Farmacologia, via Irnerio 48, Bologna BO

oppure *in streaming:*

https://teams.microsoft.com/l/meetup-join/19%3aN09c0NIyEssBnF7ObCyDOQwkgDWm1qdd9f7F2nJV9fw1%40thread.tacv2/1631519544944?context=%7b%22Tid%22%3a%22e99647dc-1b08-454a-bf8c-699181b389ab%22%2c%22Oid%22%3a%225a941351-ef41-4aa4-8771-fa50a6d62ca1%22%7d

Prof. Gaetano T. Montelione

Rensselaer Polytechnic Institute, Structural Bioinformatics Laboratory, Troy, New York, USA
(ospite Prof. Stefano Ciurli)

terrà un seminario dal titolo:

NON-STRUCTURAL PROTEIN 1 OF INFLUENZA B BINDS VIRAL 5'-TRIPHOSPHORYLATED dsRNA TO SUPPRESS RIG-I ACTIVATION AND ENHANCE VIRAL VIRULENCE

Colleghi e studenti sono cordialmente invitati

Commissione Ricerca e Attività Correlate – FaBiT

ABSTRACT

Non-structural protein 1 (NS1) of influenza virus strain B (NS1B) binds RNA and host proteins to counteract antiviral defense. While the dsRNA-binding activity of the N-terminal domain of NS1 is well established, the distinct RNA binding activity of the C-terminal domain of NS1B was only discovered recently (Ma et al, 2016). Combined Small Angle X-ray Scattering (SAXS), Nuclear Magnetic Resonance (NMR), X-ray crystallography, circular dichroism (CD), and integrative modeling of the complex formed between the C-terminal domain of NS1B (NS1B-CTD) and double-stranded (ds) -RNA reveals a blunt-end RNA binding mode reminiscent of Retinoic acid-Inducible Gene I (RIG-I) binding to 5'-triphosphorylated (5'ppp) dsRNAs, key pathogen-associated molecular pattern (PAMP) molecules which activate the host innate response to viral infection. This structural biology observation led the hypothesis that influenza B NS1 may suppress RIG-I activation by competing for 5'ppp-dsRNAs produced in the viral infection. Biochemistry studies demonstrate that NS1B-CTD binds 5'ppp-dsRNA substrates ~ 400-fold more tightly than non-phosphorylated dsRNA substrates, and further SAXS studies reveal a blunt-end binding mode of 5'ppp dsRNA in its complex with NS1B CTD. The NS1-CTD also competes with RIG-I for binding 5'ppp-dsRNA, suppressing the RNA-dependent activation of RIG-I ATPase activity. The function of the 5'ppp-dsRNA-binding activity of the NS1B CTD was further studied in cell-based viral infection assays. While RIG-I activation in viral infected cells initially leads to phosphorylation of the IRF-3 transcription factor, in wild-type virus-infected cells this phosphorylation is suppressed as the NS1B protein is expressed. However, in cells infected by a mutant virus encoding an NS1B protein with an R208A substitution that prevents 5'ppp-ds-RNA-binding, the RIG-I induced IRF-3 phosphorylation is not suppressed, leading to interferon production and apoptosis, and suppressing viral propagation. Accordingly, influenza B NS1 directly competes with innate immune receptor RIG-I in binding virally-associated dsRNA PAMPs to down-regulate the host innate immune response, enhancing the virulence of influenza B viruses.

Ma L-C; Guan R; Hamilton K; Aramini J; Mao L; Wang S; Krug RM; Montelione GT. Structure (Cell Press). 2016, 24: 1562 – 1572. A second RNA-binding site in the NS1 protein of influenza B virus. PMC5014651.

BIOGRAPHICAL SKETCH

Gaetano Montelione is an internationally recognized expert and innovator in the fields of protein NMR, structural virology, and structural bioinformatics.

Montelione carried out pioneering work on NMR pulse sequence development, including the design of the first triple-resonance protein NMR experiments with G. Wagner, as well as subsequent development of HCCcoNH-TOCSY and other widely used NMR experiments. This research lead Montelione to develop software for automated analysis of protein resonance assignments and structures. The resulting technology platform provided the basis for many key contributions by NMR to molecular biophysics, structural virology, and structural genomics research. Montelione has also made key contributions to elucidating the structural basis by which influenza viruses suppress host innate immune response, and in structure-function studies of oncogenes and tumor suppressors. Montelione is an advisor to the world-wide Protein Data Bank, and Elected Fellow of the American Association for the Advancement of Science.