Human rhinoviruses (HRVs), a major cause of the common cold, usually produce mild illness, but in asthmatics they can trigger serious exacerbations. Severe HRV infections in young children increase the odds of becoming asthmatic. HRVs belong to the Picomaviridae family and like their close relative, the poliovirus, their short, single-stranded, positive-sense RNA genomes code for one polyprotein that is cleaved by the virus’s two proteases into several viral proteins. The St. Dominic SMART Team has modeled the 2A protease (2A) of HRV2 using 3D-printing technology. 2A is a homodimer with an active site and structurally essential zinc ion in each chain [2]. 2A protease viral replication in host cells by shutting down both protein synthesis and nuclear-cytoplasmic import and signaling. By cleaving eIF4G (eukaryotic initiation factor 4G), 2A prevents localization of host mRNAs to ribosomes, which are then free to synthesize the viral polyprotein using the viral RNA’s IRES (internal ribosome entry site). When 2A cleaves specific nucleoporins (Nups) in the nuclear pore complex (NPC), proteolytic damage to Nup153, Nup50, and Nup188 inhibits immune signaling and many other cell functions. The HRV-A, HRV-B, and HRV-C species differ in their abilities to cleave both NPC nups and eIF4G. HRV-A and HRV-C 2A proteases are more efficient at cleaving Nup62 and eIF4G than HRV-B 2A proteases. Since HRV-A and HRV-C are also significantly better at triggering asthma exacerbations than HRV-B [2], it has been proposed that the effectiveness of a virus strain’s 2A protease can predict the likelihood of that strain to cause asthma exacerbations [3].

Human Rhinovirus and Its 2A Protease

Human rhinoviruses (HRVs) are a major cause of the common cold, but in asthmatics they can trigger serious life-threatening exacerbations. HRVs belong to the Picomaviridae family and like their close relative, the poliovirus, their short, single-stranded, positive-sense RNA genomes code for one polyprotein that is cleaved by the virus’ two proteases into several viral proteins. 2A protease (2A) also promotes viral replication in host cells by shutting down both protein synthesis and nuclear-cytoplasmic import and signaling. Of the three rhinovirus species (HRVA, HRVB, HRVC), recent research [3] indicates that species A and C have 2A proteases more efficient at cleaving eIF4G and Nup62 and thus are also associated with life-threatening asthma exacerbations in children [2]. It has been proposed that 2A protease may be the virulence factor that determines whether a virus causes a severe asthmatic reaction.

Cleavage of Nucleoporins (Nups) by HRV 2A Proteases

Western Blot Assessing the Ability of Different HRV 2A Proteases to Cleave Nups

Watters and Palmenburg [3]

Nup153 and Nup98: After 8 hours, 2A proteases from all three species, (HRVA, HRVB, and HRVC) cleaved all but 1 to 7% of Nup153 and Nup98.

Nup62: After 8 hours, the HRVA and HRVC 2A proteases cleaved all but 1-7% of Nup62 while 2A proteases from HRVB left almost all of Nup62 uncleaved.

Summary: The 2A proteases of HRVA and HRVC viruses were remarkably better at cleaving Nup62 than the HRVB 2A protease, which did not cleave Nup62 to a measurable extent in 8 hours.

Cleavage of Eukaryotic Initiation Factor 4G (eIF4G) by HRV 2A Proteases

Western Blot Assessing the Ability of Different HRV 2A Proteases to cleave eIF4G

Watters and Palmenburg [3]
eIF4G: After 1 hour, the two HRVA 2A proteases (16 and 89) cleaved all but 12 to 15% of eIF4G. The two HRVC (w12 and w24) cleaved all but 26 to 27%, while the HRVB (4 and 14) left 69 to 79% of eIF4G uncleaved.

Summary: HRVA and HRVC cleave 94 to 99% of eIF4G in 2hrs. In a cell, translation of mRNAs would be quickly inhibited at this rate.

2A Protease and Asthma

Human rhinoviruses have long been associated clinically with exacerbations of asthma. In this study discussed in this poster, the HRVA and HRVC species were linked to both severe asthma exacerbations [2] and were also shown to have highly effective 2A proteases at cleaving Nup 62 in the Nuclear Pore Complex and eIF4G on host mRNAs [3]. It has been proposed that the effectiveness of a virus strain’s 2A protease can predict the likelihood of that strain to cause asthma.

Conclusions

Human rhinoviruses have long been associated clinically with exacerbations of asthma. In the studies discussed in this poster, the HRVA and HRVC species were linked to both severe asthma exacerbations [2] and were also shown to have highly effective 2A proteases at cleaving Nup 62 in the Nuclear Pore Complex and eIF4G on host mRNAs [3]. It has been proposed that the effectiveness of a virus strain’s 2A protease can predict the likelihood of that strain to cause asthma.

References