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ApoL6 in Health and Disease: Insights into Cancer, HIV, Atherosclerosis, and COVID-19

Valeria Montalvo OMS II, David Ninan, DO, and Chien-An A. Hu, PhD

KHSC
KANSAS HEALTH SCIENCE CENTER

Abstract

Apolipoprotein L6 (ApoL6) is a pro-death, BH3-only and phospholipid-binding member of the Bcl-2 family. Previously, we showed that ectopic expression of ApoL6 induces mitochondria-mediated apoptosis and inflammation-induced necroptosis. Derailed apoptosis has been observed in two extremes of the disease spectrum, for example, cancer (too little apoptosis) and acute myocardial infarction (too much apoptosis). The goal of my research is to highlight ApoL6's roles in critical disease processes, such as carcinogenesis, atherosclerotic progression, dysregulated lipid metabolism, and viral infection. Better understanding of ApoL6's roles in various crucial pathways will significantly impact our understand of the pathobiology and pathophysiology of various diseases and find new routes for treatment. In this paper we will review the key roles of ApoL6 in cancer, cardiovascular disorders, and viral restriction.

Key Findings

ApoL6 in Cancer

- Recently, we and others have demonstrated ApoL6's role in cancer through two important cell processes, apoptosis and tumorigenesis.
- Compared to the ARP-246 sensitive cell lines, the insensitive cells have a way of decreasing the levels of APOL6 in the cell. Thus, preventing apoptosis and allowing tumorigenesis to progress. [1]
- ApoL6 has specific roles in regulating cell death and/or autophagy, making it a key player and target in management and treatment of cancer.

ApoL6 in Atherosclerosis

- We have shown that ApoL6 is involved in in atherosclerotic lesions, its potential as a biomarker for inflammation in patients with ST-segment myocardial infarction (STEMI), and the link of ApoL6 in cardiovascular inflammation and lesion cell apoptosis.
- ApoL6 regulates both apoptosis and autophagy in smooth muscle cells.
- ApoL6 initiates inflammatory response that upregulates proinflammatory cytokines, such as IL-1β. [6] This study showed that there were elevated levels of ApoL6 in the serum of the majority of patients with STEMI prior to reperfusion.

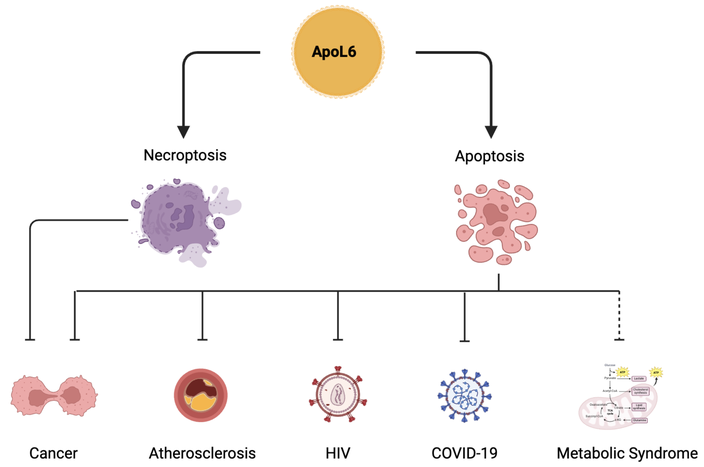

Figure 1. ApoL6 Mediates Necroptosis and Apoptosis in Various Health Conditions. This figure summarizes the role of Apolipoprotein L6 (ApoL6) in mediating necroptosis and apoptosis, and its implications in associated diseases. In essence, ApoL6 can trigger two distinct forms of programmed cell death: necroptosis and apoptosis. We showed that necroptotic Pathway is associated with Cancer, whereas apoptotic Pathway is not only associated with Cancer, but also related with atherosclerosis, HIV, COVID-19, and possibly metabolic syndrome.

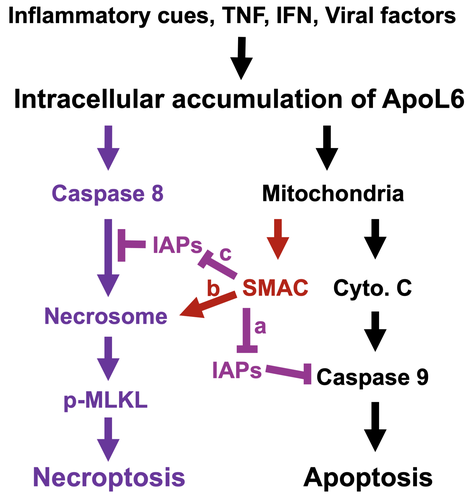

Figure 2. Hypothetical model of ApoL6-induced apoptosis in atherosclerotic lesion cells[5].

Other Key Findings

ApoL6 in HIV

- ApoL6's role in pathobiology of HIV includes antiretroviral restriction and regulation of HIV gene expression.
- APOL1 and APOL6 are 2 of the 5 factors that suppress HIV-1 infection by more than 90% in transfected 293T (human embryonic kidney cell HEK 293, T: T antigen transformed)

ApoL6 in COVID -19

- ApoL6 has also been shown to be involved in a more recent affliction of human health, COVID-19.
- It was identified that the pairing between ApoL6 and has-miR-374a-5p in the human cell is potentially disrupted by the SARS-CoV-2 virus. This ApoL6/has-miR-374a-5p pairing are potentially involved in ACE2 receptor network, regulating pro-inflammatory cytokines and in immune cell maturation and differentiation. [8]

Implications/Future Directions

Some next steps to consider would be to do a protein sequence alignment and comparison to identify how similar/different the ApoL6 of murine and humans. There have been other studies that support the role of ApoL6 in host infection. One such study done by Al-Quraishy and colleagues investigate the effect of blood-stage malaria of Plasmodium chabaudi on the DNA methylation status of host gene promoters on a genome-wide scale. [10] While investigating epigenetic changes, such as DNA methylation status, in mice in response to infection by Plasmodium chabaudi, it was discovered that the expression of several gene promotors significantly changed. One of which was APOL6 in the spleen. This could imply that APOL6 is a target for infectious diseases to enhance their pathogenesis. [10] This could also imply that similar infections from other parasites and viruses, such as COVID-19, may block or silence the expression of APOL6, thus increases their ability to infect their host. [10]

Conclusions

We and others have shown that ApoL6 is a key player in some of the most essential process that prevents disease as well as an important target for disease therapeutics. Some of the key processes that ApoL6 involves are apoptosis, autophagy, necroptosis, and viral replication. It is evident that ApoL6 deserves more attention as a potential therapeutic target for some of the most impactful diseases including cancer, HIV, atherosclerosis, and COVID-19.

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