RESEARCH PUBLICATIONS

The Immunomodulatory Metabolite Itaconate Modifies NLRP3 and Inhibits Inflammasome Activation

Abstract

The Krebs cycle-derived metabolite itaconate is highly upregulated in inflammatory macrophages and exerts immunomodulatory effects through cysteine modifications on target proteins. The NLRP3 inflammasome, which cleaves IL-1β, IL-18, and gasdermin D, must be tightly regulated to avoid excessive inflammation. Here we provide evidence that itaconate modifies NLRP3 and inhibits inflammasome activation. Itaconate and its derivative, 4-octyl itaconate (4-OI), inhibited NLRP3 inflammasome activation, but not AIM2 or NLRC4. Conversely, NLRP3 activation was increased in itaconate-depleted Irg1−/− macrophages. 4-OI inhibited the interaction between NLRP3 and NEK7, a key step in the activation process, and "dicarboxypropylated" C548 on NLRP3. Furthermore, 4-OI inhibited NLRP3-dependent IL-1β release from PBMCs isolated from cryopyrin-associated periodic syndrome (CAPS) patients, and reduced inflammation in an in vivo model of urate-induced peritonitis. Our results identify itaconate as an endogenous metabolic regulator of the NLRP3 inflammasome and describe a process that may be exploited therapeutically to alleviate inflammation in NLRP3-driven disorders.

Reference

https://www.cell.com/cell-metabolism/fulltext/S1550-4131(20)30411-3

Using the COVID-19 to influenza ratio to estimate early pandemic spread in Wuhan, China and Seattle, US

Abstract

Background: Pandemic SARS-CoV-2 was first reported in Wuhan, China on December 31, 2019. Twenty-one days later, the US identified its first case—a man who had traveled from Wuhan to the state of Washington. Recent studies in the Wuhan and Seattle metropolitan areas retrospectively tested samples taken from patients with COVID-like symptoms. In the Wuhan study, there were 4 SARS-CoV-2 positives and 7 influenza positives out of 26 adults outpatients who sought care for influenza-like-illness at two central hospitals prior to January 12, 2020. The Seattle study reported 25 SARS-CoV-2 positives and 442 influenza positives out of 2353 children and adults who reported acute respiratory illness prior to March 9, 2020. Here, we use these findings to extrapolate the early prevalence of symptomatic COVID-19 in Wuhan and Seattle.

Methods: For each city, we estimate the ratio of COVID-19 to influenza infections from the retrospective testing data and estimate the age-specific prevalence of influenza from surveillance reports during the same time period. Combining these, we approximate the total number of symptomatic COVID-19 infections.

Findings: In Wuhan, there were an estimated 1386 [95% CrI: 420-3793] symptomatic cases over 30 of COVID-19 between December 30, 2019 and January 12, 2020. In Seattle, we estimate that 2268 [95% CrI: 498, 6069] children under 18 and 4367 [95% CrI: 2776, 6526] adults were symptomatically infected between February 24 and March 9, 2020. We also find that the initial pandemic wave in Wuhan likely originated with a single infected case who developed symptoms sometime between October 26 and December 13, 2019; in Seattle, the seeding likely occurred between December 25, 2019 and January 15, 2020.

Interpretation: The spread of COVID-19 in Wuhan and Seattle was far more extensive than initially reported. The virus likely spread for months in Wuhan before the lockdown. Given that COVID-19 appears to be overwhelmingly mild in children, our high estimate for symptomatic pediatric cases in Seattle suggests that there may have been thousands more mild cases at the time.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30223-6/fulltext

Determinants of COVID-19 vaccine acceptance in the US

Abstract

Background: The COVID-19 pandemic continues to adversely affect the U.S., which leads globally in total cases and deaths. As COVID-19 vaccines are under development, public health officials and policymakers need to create strategic vaccine-acceptance messaging to effectively control the pandemic and prevent thousands of additional deaths.

Methods: Using an online platform, we surveyed the U.S. adult population in May 2020 to understand risk perceptions about the COVID-19 pandemic, acceptance of a COVID-19 vaccine, and trust in sources of information. These factors were compared across basic demographics.

Findings: Of the 672 participants surveyed, 450 (67%) said they would accept a COVID-19 vaccine if it is recommended for them. Males (72%) compared to females, older adults (≥55 years; 78%) compared to younger adults, Asians (81%) compared to other racial and ethnic groups, and college and/or graduate degree holders (75%) compared to people with less than a college degree were more likely to accept the vaccine. When comparing reported influenza vaccine uptake to reported acceptance of the COVID-19 vaccine: 1) participants who did not complete high school had a very low influenza vaccine uptake (10%), while 60% of the same group said they would accept the COVID-19 vaccine; 2) unemployed participants reported lower influenza uptake and lower COVID-19 vaccine acceptance when compared to those employed or retired; and, 3) Black Americans reported lower influenza vaccine uptake and lower COVID-19 vaccine acceptance than all other racial groups reported in our study. Lastly, we identified geographic differences with Department of Health and Human Services (DHHS) regions 2 (New York) and 5 (Chicago) reporting less than 50 percent COVID-19 vaccine acceptance.

Interpretation: Although our study found a 67% acceptance of a COVID-19 vaccine, there were noticeable demographic and geographical disparities in vaccine acceptance. Before a COVID-19 vaccine is introduced to the U.S., public health officials and policymakers must prioritize effective COVID-19 vaccine-acceptance messaging for all Americans, especially those who are most vulnerable.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30223-6/fulltext

Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans

Abstract

COVID-19 represents a global crisis, yet major knowledge gaps remain about human immunity to SARS-CoV-2. We analyzed immune responses in 76 COVID-19 patients and 69 healthy individuals from Hong Kong and Atlanta. In PBMCs of COVID-19 patients, there was reduced expression of HLA-DR and pro-inflammatory cytokines by myeloid cells, and impaired mTOR-signaling and IFN-α production by plasmacytoid DCs. In contrast, there were enhanced plasma levels of inflammatory mediators, including EN-RAGE, TNFSF14, and oncostatin-M, which correlated with disease severity and increased bacterial products in human plasma. Single-cell transcriptomics revealed no type-I IFN, reduced HLA-DR in myeloid cells of severe patients, and transient expression of IFN-stimulated genes. This was consistent with bulk PBMC transcriptomics, and transient, low plasma IFN-α levels during infection. These results reveal mechanisms and potential therapeutic targets for COVID-19.

Reference

https://science.sciencemag.org/content/early/2020/08/10/science.abc6261

Virtual screening, molecular docking studies and DFT calculations of FDA approved compounds similar to the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was confirmed as the causative virus of COVID-19 disease, which is currently a worldwide pandemic. Efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is one of the most potent chemical compounds proposed to treat COVID-19 infection. We, therefore, performed virtual screening on FDA approved drugs that are similar to the efavirenz moiety. Subsequently, the compounds were subjected to screening by analyzing their drug-likeness, such as Lipinski's rule of five and ADMET properties. Molecular docking study revealed that Met165, His41, His163, and Phe140 were important interacting residues for COVID-19 main protease receptor-ligand interaction. Five top-ranked compounds, podophyllotoxin, oxacillin, lovastatin, simvastatin, and gefitinib, were selected by virtual screening and docking studies. The highest occupied molecular (HOMO) orbital, lowest unoccupied molecular orbital (LUMO) and energy gap values was calculated using density functional theory (DFT). The results of the study showed that lovastatin and simvastatin might be considered as lead compounds for further development for COVID-19 main protease inhibitors.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(20)31486-9

Study of the structural, chemical descriptors and optoelectronic properties of the drugs Hydroxychloroquine and Azithromycin

Abstract

Density functional theory (DFT) was performed in order to predict the structural, chemical descriptors and optoelectronic properties of the drugs Hydroxychloroquine and Azithromycin using the wB97XD, O3LYP and B3LYP functional with 6-31+G(d,p) basis

set. It is observed from our studies that most of the descriptors presented show association with some processes, including absorption, blood-brain barrier transport, binding and even toxicity. Hence, the treatment of COVID-19 using Hydroxychloroquine and Azithromycin in some patients as single dose and their combination in patients with Corona virus resistance can be more effective. Our results show that these therapeutic molecules may also have good nonlinear optical applications, may have semiconductor character with wide band gap and can also be promising materials in the production of optoelectronic devices. The density of states and thermodynamic properties were equally determined.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(20)31491-2

Correlates of access to hand hygiene resources in Ghanaian households: An exploratory analysis of the 2014 demographic and health survey

Abstract

Objectives: Handwashing with soap and water remains the most effective public health measure to reduce the risk of infectious diseases, which kill over 2.5 million people annually, mostly children in developing countries. The absence of hand hygiene resources in homes put many at risk of these infectious diseases. In the wake of the outbreak of the COVID-19 pandemic, the World Health Organization (WHO) and governments around the world have stressed the importance of regular handwashing to prevent the spread of the virus. This suggests that research on water, sanitation, and hygiene issues deserve continuous scholarly attention. In Ghana, studies on household's access to hand hygiene resources are few and relatively old. Therefore, this study estimated the proportion of Ghanaian households with access to hand hygiene resources and their associated determinants using data from a recent national survey.

Methods: The study used the cross-sectional 2014 Ghana Demographic and Health Surveys dataset. We used STATA-14 to perform data analyses on a weighted sample

of 11,710.06 households. We used complex samples analysis technique to adjust for sample units, stratification and sample weights for both the descriptive statistics and multivariate robust Poisson regression.

Results: The result showed that about one fifth of Ghanaian households had access to hand hygiene resources. Households with heads who attained a Middle/JHS/JSS or Secondary/SSS/SHS/Higher level education, those headed by persons having at least 30–44 years, and non-poorest households, and from the Volta region were more likely to have access to hand hygiene resources. Further, households in urban areas, households that spent between 0-30 min to get to a source of water, and households in Eastern and Brong-Ahafo regions were less likely to have access to hand hygiene resources.

Conclusion: This study identified key socioeconomic and demographic correlates of a household's access to hand hygiene resources in Ghana. In the interim, the government and development partners can provide hand hygiene resources to households with limited or no access. For the long term, we recommend that the government should implement measures and policies that facilitate citizens' economic independence and their attainment of higher formal education.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(20)31527-9

Publication Date: Aug 06, 2020

Predicting novel drugs for SARS-CoV-2 using machine learning from a >10 million chemical space

Abstract

There is an urgent need for the identification of effective therapeutics for COVID-19 and we have developed a machine learning drug discovery pipeline to identify several drug candidates. First, we collect assay data for 65 target human proteins known to interact with the SARS-CoV-2 proteins, including the ACE2 receptor. Next, we train machine learning models to predict inhibitory activity and use them to screen FDA registered

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chemicals and approved drugs (~100,000) and ~14 million purchasable chemicals. We filter predictions according to estimated mammalian toxicity and vapor pressure. Prospective volatile candidates are proposed as novel inhaled therapeutics since the nasal cavity and respiratory tracts are early bottlenecks for infection. We also identify candidates that act across multiple targets as promising for future analyses. We anticipate that this theoretical study can accelerate testing of two categories of therapeutics: repurposed drugs suited for short-term approval, and novel efficacious drugs suitable for a long-term follow up.

Reference

Kowalewski, Joel, and Anandasankar Ray. "Predicting novel drugs for SARS-CoV-2 using machine learning from a> 10 million chemical space." *Heliyon* (2020): e04639.

Searching potential antiviral candidates for the treatment of the 2019 novel coronavirus based on DFT calculations and molecular docking

Abstract

In the present work, the succinic acid (SA), L-pyroglutamic acid (L-PGA), N-phenyl-thioacetamide (N-NPTA), 2-amino-5-chloropyridine hydrogen succinate (ACPS), epigallocatechine Gallate (EGCG) or KDH and, selenomethionine (SeM) compounds have been proposed as potential antiviral candidates to treatment of COVID-19 based on B3LYP/6-311++G∗∗ calculations and molecular docking. Solvation energies, stabilization energies, topological properties have been evaluated as function of acceptors and donors groups present in their structures. ACPS presents the higher reactivity in solution possibly because has the higher nucleophilicity and elecrophilicity indexes while KDH evidence the higher solvation energy probably due to the higher quantity of donors and acceptors groups. NBO studies show that KDH is the most stable in solution. Mapped MEP surfaces have evidenced stronger nucleophilic and electrophilic sites in ACPS, in agreement with the three C=O and two N–H and O–H groups present in this species while KDH has only a C=O group but a total of 19 acceptors and donors groups. From the above studies for six species we can propose that the better potential antiviral candidate to treatment of COVID-19 is ACPS and then, KDH. For a better prediction of the antiviral and anti-inflammatory properties of the

proposed compounds, molecular docking calculations were performed by using four structures of COVID-19. Docking results were discussed basing on binding affinities and the interaction types among ligands and different amino acid residues, indicating the powerful ability of KDH and then ACPS ligands on front of the novel coronavirus disease especially for the first and the fourth species (6LU7, 7BTF).

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(20)31484-5

REPORT

A molecular pore spans the double membrane of the coronavirus replication organelle

Coronavirus genome replication is associated with virus-induced cytosolic double-membrane vesicles, which may provide a tailored micro-environment for viral RNA synthesis in the infected cell. However, it is unclear how newly synthesized genomes and mRNAs can travel from these sealed replication compartments to the cytosol to ensure their translation and the assembly of progeny virions. Here, we used cellular electron cryo-microscopy to visualize a molecular pore complex that spans both membranes of the double-membrane vesicle and would allow export of RNA to the cytosol. A hexameric assembly of a large viral transmembrane protein was found to form the core of the crown-shaped complex. This coronavirus-specific structure likely plays a critical role in coronavirus replication and thus constitutes a potential drug target.

Reference

https://science.sciencemag.org/content/early/2020/08/05/science.abd3629

PERSPECTIVE

Interferon responses in viral pneumonias

Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak quickly developed into a pandemic in March 2020. To date, no vaccines or antiviral medications are available, and given the urgency, many clinical trials have started screening existing antiviral drugs for efficacy against SARS-CoV-2 infection. Among a variety of therapeutic approaches, the use of different types of interferon (IFN) as antiviral agents is under investigation owing to promising outcomes in other coronavirus-induced pathologies. Through different mechanisms and effector proteins, IFNs play an important role in the inhibition of viral replication. Major group, and Broggi group, respectively, described the mechanisms by which IFN-λ responses contribute to pathogenesis in viral pneumonias. Conversely, Hadjadj and co-workers studied peripheral blood responses from a cohort of 50 patients with coronavirus disease 2019 (COVID-19), demonstrating that critically ill patients have reduced IFN responses paired with a proinflammatory response. For more details, read the link given below.

Reference

https://science.sciencemag.org/content/369/6504/626

COMMENT

Some challenges of sparse data necessitating strong assumptions in investigating early COVID-19 disease

Abstract

In this study (published in EClinicalMedicine), Du and co-workers use a novel approach to estimate unseen COVID-19 cases early in the pandemic, when neither awareness of the disease nor suitable testing was available. By retrospectively testing samples from patients seeking treatment for seasonal flu, then calculating the 'COVID-19-to-influenza positives ratio' (CIPR) of SARS-CoV-2 positives to flu positives, and applying the CIPR to observed flu cases, they extrapolate the likely unseen COVID-19 cases.

This method requires many strong assumptions, and generates imprecise estimates given few observed infective events, and is subject to several different selection biases. Such estimates are needed, since for a new virus, accurate assessment of onset date and early transmission dynamics are difficult. These early data are needed to understand pandemic development, and for predicting onset and containing new infective waves in space and time, with localised outbreaks probable. Therefore, it is necessary to understand the influence of both strong assumptions and sparse data on model outputs and interpretation. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30243-1/fulltext

WORLD VIEW

A negative COVID-19 test does not mean recovery

Eight months into the global pandemic, its effects are measured only in deaths. Non-hospitalized cases are loosely termed 'mild' and are not followed up. Recovery is implied by discharge from hospital or testing negative for the virus. Ill health in those classed as 'recovered' is going largely unmeasured. And, worldwide, millions of those still alive, who got ill without being tested or hospitalized are simply not being counted.

Previously healthy people with persistent symptoms, such as chest heaviness, breathlessness, muscle pains, palpitations and fatigue, which prevent them from resuming work or physical or caring activities, are still classed under the umbrella of 'mild COVID'. Data from a UK smartphone app for tracking symptoms suggests that at least one in ten of those reporting are ill for more than three weeks. Symptoms lasting several weeks and impairing a person's usual function should not be called mild.

Defining and measuring recovery from COVID-19 should be more sophisticated than checking for hospital discharge, or testing negative for active infection or positive for antibodies. Once recovery is defined, COVID can be differentiated that quickly goes away from the prolonged form.

For surveillance, public-health agencies must prioritize agreement on criteria for a definition of recovery, and on the structures in which these criteria could be implemented. Research must be overlaid on surveillance with studies of the characteristics of those experiencing prolonged ill health.

The narrow narrative of death as the only bad outcome from COVID needs broadening to include people becoming less healthy, less capable, less productive and living with more pain. For that, we'll need better surveillance. The essential first step is getting clear and universal definitions for recovery and COVID severity. For more details, read the link given below.

Reference

https://www.nature.com/articles/d41586-020-02335-z

EDITORIAL

How to stop COVID-19 fuelling a resurgence of AIDS, malaria and tuberculosis

AIDS, malaria and tuberculosis (TB), three of the deadliest infectious diseases, together kill 2.4 million people every year, with TB alone responsible for 1.5 million deaths. And deaths from these diseases could almost double over the next year, according to the Global Fund to Fight AIDS, Tuberculosis and Malaria, a consortium of donors that funds treatments. The reason: coronavirus. It's a horrifying prospect, and calls for an urgent action plan.

More than three months of lockdowns have prevented many people from accessing treatments for non-COVID infectious diseases; at the same time, new cases of these illnesses will have gone undetected. Although lockdowns are easing, it will take some time for health care to get back to normal, as authorities continue to prioritize COVID-19. Taken together, this is resulting in a surge of cases.

That's why there needs to be a step change in funding for AIDS, malaria and TB prevention, treatment and research, and greater public awareness of the rising threat posed by infectious diseases. And researchers — particularly epidemiologists — must continue to refine the models that are alerting the world to this approaching catastrophe.

Reference

https://www.nature.com/articles/d41586-020-02334-0