Smoking in the age of COVID: Some immunological considerations

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Many have been wondering how smoking might affect the risk of suffering from COVID-19. It has been well established that smoking increases an individual's risk of developing respiratory infections. Cigarette smoking, for example, increases the risk of developing influenza by a factor of five when compared to non-smokers.

This relationship is due to a variety of factors ranging from chronic bronchitis and inflammation of the lungs as a result of inhaling smoke to dysregulation of the immune system (in particular the innate immune system), and holds true for cigarette smoke, e-cigarettes, and largely for marijuana usage as well.

A recent survey has shown that individuals who use cigarettes, e-cigarettes, or both are at significantly higher risk to be diagnosed with COVID-19. This study , published in the *Journal of Adolescent Health*, found that cigarette smokers are 2.3 times more likely to be diagnosed with COVID-19 than non-smokers, whereas individuals who use e-cigarettes only are five times more likely, and individuals who use both are seven times more likely. A meta-analysis has shown that cigarette smoking also significantly increases the risk of disease progression in individuals who develop COVID-19.

There are several immunological factors contributing to an increased likelihood of developing COVID-19 and increased severity of cases in smokers. The receptor responsible for allowing SARS-CoV-2, the causative agent of COVID-19, to enter human cells is ACE2. The enzyme on the surface of human cells that primes the spike protein of SARS-CoV-2 in order for it to fuse with ACE2 is TMPRSS2.

A new preprint has demonstrated that smoking upregulates the expression of both ACE2 and TMPRSS2 on the surface of cells. This increased expression would increase the number of binding domains and priming capability available to SARS-CoV-2, making it much easier for the virus to enter the cells.

Once in the cells, the virus essentially converts the infected cell into a virus-producing machine. Early in the infection, our innate immune cells will destroy any cells that they think are infected. This is an essential function for viral clearance, and primarily takes place before the immune system has specifically identified what the pathogen is.

Much of the damage associated with coronavirus infections is actually done by the immune system itself. Basically, what happens is that the innate immune cells overreact and begin releasing large amounts of proinflammatory cytokines and effector molecules, which causes massive inflammation and cell damage.

Smoking causes chronic inflammation in the lungs as well as upregulation of innate defense proteins, meaning that not only are the lung cells damaged before COVID-19 infection, but subsequent infection causes more severe innate immune cell overreaction than in non-smokers, thus leading to more lung damage and more severe disease.

Recently, it has also been found that e-cigarettes also increase these innate defense proteins and activation markers, particularly those of neutrophils which contribute significantly to lung damage in COVID infections, similar to that seen in cigarette smokers.

In addition, e-cigarettes have been found to alter mucin (the gel forming protein in lungs, the major constituent of mucous in the lungs) secretion and concentration in highly similar ways to traditional cigarettes. High levels of these mucins in the lungs of

COVID patients have been linked to severe respiratory distress.

It is highly probable, though not confirmed experimentally, that having elevated levels of these mucins present in the lungs before COVID-19 infection, due to a history of tobacco or e-cigarette use, increases the risk for severe respiratory distress in an individual once they contract coronavirus.

Perhaps the most interesting case is marijuana. CBD, the non-psychotropic component of cannabis that is sought in medicinal uses, is a well-known immunomodulator, meaning that it alters the regulation of the immune system in some ways. No data is yet available on the effect of marijuana on the severity of COVID-19 infections, but it can be proposed that there would actually be differing effects depending on the disease stage.

CBD acts as an anti-inflammatory agent and an immunosuppressant, and therefore early on in the infection may actually prevent the innate immune cells from responding to and clearing the virus efficiently, leading to disease progression and increase in its duration.

However, in late stage infection, the innate immune cells themselves are causing much of the damage, and therefore the anti-inflammatory and immunosuppressive effects may actually prevent cellular damage. CBD has been found to have these protective effects against damage done by immune cells overreacting to several respiratory viruses, and may play a similar role here.

While there is little data on the effect of marijuana usage on COVID-19 severity, a preprint has shown that marijuana usage correlates with an increased risk of developing a COVID infection. It is not known whether this increased risk is due to chronic, low-level bronchitis due to inhalation of marijuana smoke, the immunosuppressive effects of CBD, unknown effects on the ACE2 receptor and TMPRSS2 (as seen in tobacco and e-cigarette usage), or social factors associated with marijuana usage. Nonetheless, the findings are worth considering.

It is critical that individuals know the factors that put them at increased risk for contracting coronavirus, as well as for developing severe disease once infected. Based on the current data, tobacco and e-cigarette usage are both associated with increased risk of developing COVID-19 infection, and both are highly likely to contribute to progression to severe disease in infected individuals.

Less is known about the effects of marijuana usage. While marijuana use has been found to correlate with increased risk of developing COVID-19, for reasons currently unknown, no data is available on the effect of marijuana on the severity of disease, though it can be hypothesized that contradictory immunological effects would take place depending on the stage of the viral infection.