More questions than answers, and a way ahead

Editoriale

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A wealth of articles, reviews and data are being published on the most prestigious international journals, gradually shedding light on this new pneumonia and its associated renal complications. Way more rapidly, however, our day-to-day experience is forcing us to grapple with this pandemic and gives us glimpses into this new pathological condition.

Covid-19 is spreading quickly in a human population that lacks any kind of immunity. This viral infection has a high mortality rate, especially among the elderly, among people with underlying acute and chronic conditions such as chronic obstructive pulmonary disease, hypertension, diabetes, ischemic heart disease, advanced CKD, and among dialysis and kidney transplant recipients (but, according to current data, not liver transplant recipients). Many more cases, although it is impossible to know how many, present very mild or no symptoms and do not require any medical attention. Clearly, the disease progression is extremely diversified and ultimately depends on the interaction between each individual host and the virus. To try and understand this variability, we need to look not only at comorbidities, but also at the sequence of events taking place once Covid-19 enters the body:

a) it is recognized by the innate immune system through pattern recognition receptors (PRRs);
b) it induces a higher expression of inflammatory cytokines, the maturation of dendritic cells and the subsequent synthesis of interferon, which should limit the spread of the virus within the body and accelerate macrophage phagocytosis (but it produces a specific protein, *protein N*, that seem to help the virus escaping this first defence mechanism);
c) adaptive immune response kicks in, with *CD4+ e CD8+* T-cells amplifying the inflammatory response;
d) evidence shows that Covid-19 can inhibit T-cells and induce their apoptosis, with direct complement activation and the formation of the membrane attack complex.

When the response to the infection is inadequate, an uncontrollable inflammatory response may ensue. In a non-negligible number of cases, this response ends up leading to the most nefarious consequences for the patient, with the onset of pulmonary lesions and multiple organ dysfunction syndrome that does not respond to treatment.

In the worst-case and most lethal scenario there is an aberrant and prolonged production of inflammatory cytokines by dendritic cells and macrophages; none of this is observed in the less severe forms, where symptoms are limited or absent.

The several phenotypes that are being identified in the scientific literature appear rather difficult to distinguish in the clinical practice. The key factors underlying the different clinical-

pathological responses are:

1. **where the virus replicates**: in type I and type II pneumocytes in the most severe cases, in the epithelium of the upper respiratory tract in the less severe;
2. **the speed of viral replication**: fast replication induces morphological changes in infected cells and a high production of inflammatory cytokines, with the migration of inflammatory cells to the lungs. A correlation between speed of replication, inflammatory response and disease severity has been demonstrated both in experimental models and in humans. Furthermore, fast replication has been linked to an increased production of interferon-inhibiting proteins that block the innate immune response;
3. **the individual specificities**: in experimental models, different types of mice react differently in terms of response and disease severity;
4. **the immune system *maturity*** could explain why the response to the viral infection varies widely: innate immune response activation is less efficient in the elderly, as is the ability to respond to infections in general;
5. **the direct action of the virus,** which can induce T-cell apoptosis and activate the alternative complement pathway.

Our collective experience seems to show that intervening promptly with targeted drugs, or with drugs capable of slowing and reducing the strength of the virus early on, are the most promising starting point to try and suggest evidence-based therapeutic approaches.

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