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Diabetes and COVID-19: The potential role of mTOR

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ABSTRACT

Diabetes is the most frequent comorbidity among patients with COVID-19. COVID-19 patients with diabetes have a more severe prognosis than patients without diabetes. However, the etiopathogenetic mechanisms underlying this more unfavorable outcome in these patients are not clear. Probably the etiopathogenetic mechanisms underlying diabetes could represent a favorable substrate for a greater development of the inflammatory process already dysregulated in COVID-19 with a more severe evolution of the disease. In the attempt to shed light on the possible etiopathogenetic mechanisms, we wanted to evaluate the possible role of mTOR (mammalian Target Of Rapamycin) pathway in this context.

We searched the PubMed and Scopus databases to identify articles involving diabetes and the mTOR pathway in COVID-19.

The mTOR pathway could be involved in this etiopathogenetic mechanism, in particular, the activation and stimulation of this pathway could favor an inflammatory process that is already dysregulated in itself, while its inhibition could be a way to regulate this dysregulated inflammatory process. However, much remains to be clarified about the mechanisms of the mTOR pathway and its role in COVID-19.

The aim of this review is to to understand the etiopathogenesis underlying COVID-19 in diabetic patients and the role of mTOR pathway in order to be able to search for new weapons to deal with this disease.

1. mTOR pathway and COVID-19

mTOR (mammalian Target Of Rapamycin) is a crucial pathway in many physiological processes, such as cell cycle progression, transcription, translation, differentiation, apoptosis, motility and cell metabolism. mTOR plays a central role in the regulation of cell growth and proliferation, at the translational level, and in cell cycle progression, in particular, mTOR also modulates protein synthesis through regulation of RNA polymerases I and III, which are responsible for ribosomal and transfer RNA transcription (Fig. 1). It is known that the mTOR pathway plays a fundamental role in viral translation [1]. It is already known that several viruses such as Adenovirus, Cytomegalovirus, Herpesvirus and the same Middle Eastern Respiratory Syndrome Coronavirus (MERS – CoV) use the mTOR pathway to be able to replicate [2,3]. In particular, the mTOR pathway also appears to be involved in the life cycle of SARS-CoV-2 infection [4]. The antiviral properties of mTORis have been known and ascribed to a variety of mechanisms [5].

Blockade of the mTOR pathway induces an inhibition of protein synthesis and prevents the activation of lymphocytes [6,7]. Furthermore, it inhibits the expression of proinflammatory cytokines, such as IL-2, IL-6 and IL-10 and suppresses the cytokine storm [2]. These data were observed with the use of rapamycin, an inhibitor of the mTOR pathway. In particular, rapamycin is able to interrupt the cell cycle of T cells during their transition from G1 to S phase by inhibiting signal-mediated interleukin [8–11]. The authors Husain and Byrareddy evaluated the different uses of Rapamycin, highlighting that this drug with its action can help control the synthesis of viral particles, cytokine storms and helps fight the disease thanks to its anti-aging effects [4]. Maiese et al. showed that mTOR pathways in combination with AMPK (Adenosine Monophosphate-activated Protein Kinase) may offer valuable targets for controlling cell damage, oxidative stress, mitochondrial dysfunction and the onset of hyperinflammation, a significant dysregulation associated with COVID-19 [5]. mTOR inhibitors in preventing COVID-19 severity were examined in an article by Zheng et al., where

Abbreviations: mTOR, mammalian Target Of Rapamycin; SARS-CoV-2, Severe Acute Respiratory Syndrome – CoronaVirus2; COVID-19, COronaVIrus Disease-19.

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the potential role of these drugs in reducing the possible development of the dysregulated inflammatory process was shown and therefore their possible role in preventing severe forms of disease was hypothesized [12]. This hypothesis was based on the ability of mTOR inhibitors to limit the proliferation of memory B cells and T cell responses [10]. Ramaiah et al. showed a potential action of rapamycin in inhibiting SARS-CoV-2 infection and replication in human lung cells [13,14]. Sargiacomo et al. evaluated the use of azithromycin, doxycycline and rapamycin, drugs that inhibit protein synthesis, demonstrating that these drugs reduced inflammation and viral replication. Mechanistically, this is due to the fact that cytokines and viruses are both made up of proteins. Both use cellular ribosomes for protein translation [15].

The inhibitory action on the mTOR pathway can help control the synthesis of viral particles and regulate cytokine storms [16–18]. mTOR inhibitors also suppress early B cell production and reduce antigen-specific memory B cell populations. Therefore, SARS-CoV-2 infected patients treated with mTOR inhibitors can be expected to have reduced early cross-reactive antibody production and thus less antibody-dependent enhancement. Therefore, mTOR inhibitors could act as a double-edged sword in COVID-19 patients [19,20].

From the various studies reported it emerges that the inhibitory drugs of the mTOR pathway, through the regulation of T cells, the reduction of viral replication and the reduction of the production of pro-inflammatory cytokines, would seem to be able to play a role in the regulation and management of that inflammatory process [21].

2. Outcomes of COVID-19 infection in patients with diabetes

It is well known that patients suffering from COVID-19 (CoronaVIrus Disease-19 (COVID-19) with diabetes have a poorer prognosis than patients without diabetes. In fact, the disease is more severe and the mortality rate higher in patient with diabetes than in those without [22–25]. In addition hyperglycemia, regardless of the diagnosis of diabetes, has been implicated in a poor prognosis in patients with COVID-19 [26,27]. A prevalence of about 10% of diabetes has been reported in patients with COVID-19, thereby constituting the most frequent co-morbidity [28–30]. Moreover, this prevalence fluctuated between 7% and 21% [10]. The prevalence of diabetes in COVID-19 patients varied widely depending on the geographic areas considered [31,32]. Additionally, patients with diabetes and COVID-19 have an approximately three times greater relative risk of developing serious disease and a higher mortality rate than patients with COVID-19 and without diabetes. [33–38]. Several studies compared COVID-19 patients with diabetes to those without. A retrospective observational study from 88 US hospitals (n = 570), showed a significant increase in death rate in patients with diabetes compared to those without (28.8% versus 6.2%, $p < 0.001$) [27]. A higher death rate was reported in patients with COVID19 who had uncontrolled hyperglycemia (n = 184) (41.7 versus 14.8%, $p < 0.001$) [39,40]. Furthermore, the patients with diabetes had greater odds of ICU (Intensive Care Unit) admission (OR 1.59, 95% CI 1.01–2.52), mechanical ventilation (OR 1.97, 95% CI 1.21–3.20), and death (OR 2.02, 95% CI 1.01–4.03) [22]. A retrospective study (n = 7,337) highlighted increased mortality in COVID-19 patients with diabetes (n = 810) compared to those without (n = 6,385) (HR 1.49, 95% CI 1.13–1.96, p = 0.005) [41]. Another study showed an independent association of glycemic control to increased mortality in people with COVID-19 [42]. However, the etiopathogenetic mechanisms underlying this more unfavorable outcome in this category of patients are not very clear.

3. Insulin and COVID-19

In several studies, the potential etiopathogenetic role of insulin in patients with COVID-19 and type 2 diabetes mellitus has been noted. In particular, it has been observed that, following the immune activation, lymphocytes overexpress insulin receptors and therefore dysregulated insulin signaling in immune cells could be involved in the dysregulated immune response in patients with COVID-19 and diabetes, explaining the unfavorable outcome. In fact, insulin would be able to activate and stimulate the PI3K/Akt/mTOR pathway (Phosphatidyl Inositol 3-

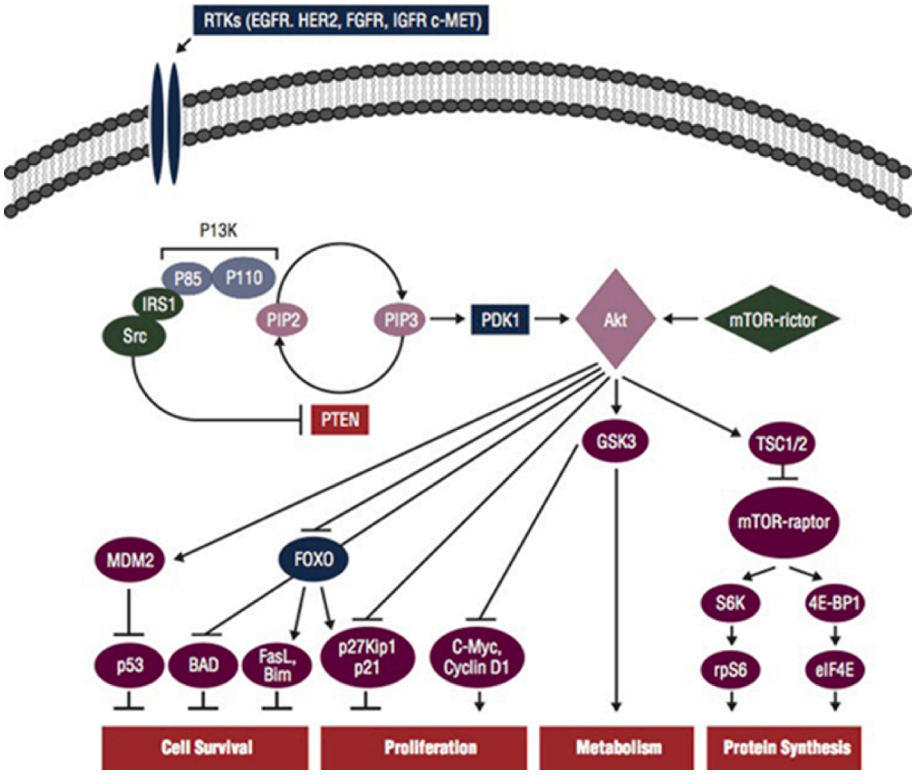

Fig. 1. PI3K/Akt/mTOR pathway.

Kinase/AKT/ mammalian Target Of Rapamycin pathway), which is involved both in the regulation of cells of the immune system, in particular by determining their metabolic activity, their survival and their differentiation, which in processes related to viral infections [43]. Through this pathway, insulin would be able to regulate a series of activities, in particular, transcriptional activity [44]. Therefore, insulin seems to have a role not only in metabolic activity, but it would also seem to have a role in regulating the immune response. In fact, its possible role in the Notch signaling is hypothesized. In particular, the Notch signaling pathway is involved in various immune functions, including antigen presentation by mast cells and their activation, activation and differentiation of T cells [45]. The cells of the immune system, in particular, macrophages and neutrophils, express the receptors for insulin and the stimulation of these receptors by insulin, would seem to favor the release of TNF and IL-6, hypothesizing a possible pro-inflammatory insulin [46]. This pro-inflammatory activity would appear to be carried out through the activity of hypoxia-inducible factor 1-alpha (HIF-1 alpha), in particular through the induction and stimulation of the expression of hypoxia-inducible factor 1-alpha. (HIF-1 alpha). This expression would be induced through the activation of the PI3K/Akt/mTOR pathway, which, through the activation and regulation of transcriptional processes, would favor the production of hypoxia-inducible factor 1-alpha (HIF-1 alpha) [47]. In turn involved in the production of pro-inflammatory cytokines involved in the immune response [48]. Furthermore, insulin would play a fundamental role too in activating the functionality of T cells and this role is achieved by stimulating the pathway PI3K/Akt/mTOR [49]. Another possible pro-inflammatory action by insulin could be carried out by stimulating Akt activity, resulting to phosphosphorylation of FOXO proteins and reduced activity and functionality of regulatory T cells. T reg cells, with a downregulation of insulin receptors, seem to play an anti-inflammatory role [50]. Furthermore, various immune cells also express IGF-1 receptors, which also activate the PI3K/Akt/mTOR pathway. In this respect, both the IGF-1 receptor and the insulin/IGF-1 hybrid receptors can be activated by insulin; however, at different affinities and at elevated insulin levels, insulin can also bind and activate IGF-1 receptors [51]. These observations are also relevant to insulin as they suggest that hyperinsulinemia, which can be very pronounced in ICU patients, may also involve IGF-1 signaling. Hence, insulin can exert an immune-regulating effect even in immune cells with a low abundance of insulin receptors [52]. In relation to what has been said above, it is clear that hyperinsulinemia could favor the inflammatory process through the stimulation of the mTOR pathway, inducing a worsening of the outcome of these patients. After all, at the base of COVID-19, there is a virus-induced dysregulated inflammatory process, in which hyperinsulinemia could act in an unfavorable way, promoting the dysregulated inflammatory process.

At the same time, the question arises of the role of insulin resistance, which is often found in long-standing diabetic patients and which theoretically should induce an altered and reduced signal related to insulin stimulation. However, there are conflicting data in this regard and the need to prove everything [53].

Furthermore, the role of hyperglycemia in this category of patients should be clarified. In that, hyperglycemia could induce an up-regulation of mTOR receptors and therefore, favor the inflammatory stimulus by insulin [47,54]. This hypothesis would be based on the fact that the mTOR pathway plays a fundamental role in cellular metabolism and that hyperglycemia could represent a stimulus for the greater use of this pathway [47]. At the same time, the up-regulation of mTOR receptors could not only constitute a greater inflammatory stimulus by insulin, but at the same time could represent a pathway favoring viral replication [5]. In fact, the mTOR pathway represents a fundamental pathway in the processes of protein synthesis and transcription [5,47].

Therefore, as reported above, it can be deduced that the etiopathogenetic mechanisms underlying diabetes could represent a favorable substrate for a greater development of the inflammatory process already dysregulated in COVID-19 with a more severe evolution of the disease. However, numerous other studies are needed to demonstrate such correlations.

4. Metformin and COVID-19

Among the oral antidiabetic drugs, the most prescribed in the world is metformin, which is characterized by a high efficacy, low cost, good tolerability profile. In general, metformin acts by reducing the levels of postprandial insulin and peripheral insulin resistance, thus leading to a reduction in blood sugar without causing clinically significant hypoglycemia; therefore, it acts as an anti-hyperglycemic agent and peripheral insulin sensitizer. Although it was introduced in the 1950s, its mechanism of action is still not completely clear today and it also seems to involve the inhibition of the mitochondrial respiratory chain, as demonstrated in various organs and tissues including hepatocytes, skeletal muscle, endothelial cells, bilio-pancreatic and neuronal cells [55,56,57]. Its mechanism of action seems to be partly realized through the inhibition of key genes of cellular metabolism, among which, the most studied are those of the PI3K/Akt/mTOR pathway which through the activation of TSC2 (Tuberous Sclerosis Complex 2, tuberine) negatively regulate the activity of mTOR [58,59]. (Fig. 2) A possible anti-inflammatory action of metformin is already known in the literature, in fact, Isoda et al. demonstrated that metformin reduced IL-1β excretion and inhibited nuclear translocation of nuclear factor kB (NF-kB), inducing anti-inflammatory activity through inhibition of the mTOR pathway [60].

Several studies have evaluated the impact of metformin in patients with COVID-19 suffering from diabetes. Among the categories of patients considered, this drug has been re-evaluated for its immunomodulatory action [61–69]. A retrospective study of 6,256 patients with type 2 diabetes and COVID-19 showed a 24% RR reduction in mortality (HR 0.76, 95% CI 0.60–0.96, $p = 0.02$) in patients using metformin versus those not using it. The CORONADO study found that patients who were being treated with metformin reported lower mortality [22]. Another study, on the other hand, did not observe differences in mortality between those who used Metformin and those who did not [67]. Some meta-analyzes performed in this regard also found a significant reduction in the risk of death among metformin users compared to non-users [70–72].

5. Other antidiabetic medications and COVID-19

Besides metformin, other anti-diabetic drugs also act on the mTOR signaling pathway.

In particular, Pioglitazone is known to protect against hypoxemia/

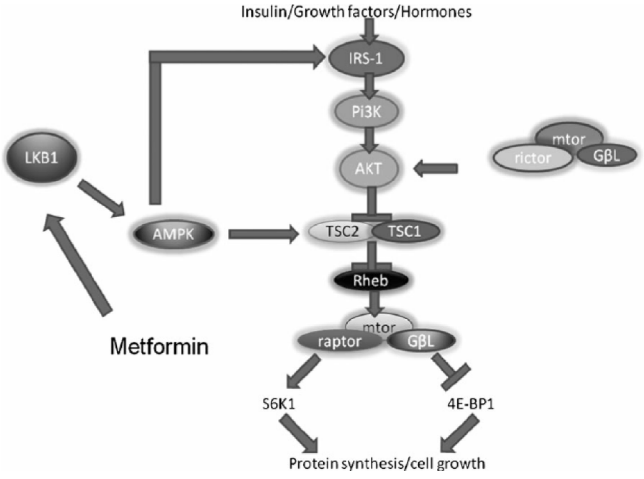

Fig. 2. Metformin and mTOR pathway.

reoxygenation lesions by potentiating autophagy through the AMPK-mTOR signaling pathway [73]. The study of Xiaoqing Xi et al. has shown that pioglitazone, a PPAR-γ agonist used in the treatment of type 2 diabetes, could protect against ischemic renal disease by inhibiting renal cell apoptosis and enhancing antioxidant effect. Furthermore, the same study demonstrated that pioglitazone significantly protected against H/R injury by enhancting autophagy in a normal rat kidney proximal tubular cells NRK-52E model of H/R. The mechanisms underlying the cytoprotective effect of pioglitazone was due to Pioglitazone's promotion of cell autophagy through the AMPK/mTOR pathway. Activation of AMPK could inhibit mTOR and stimulate autophagy. Thus autophagy may participate in pioglitazone-induced cytoprotection against H/R damage in NRK-52E cells. Regulation of autophagy could represent a new strategy in the treatment of ischemic kidney disease [73]. Therefore, also Pioglitazone, could through its mechanism of action indicated above represent a further weapon in the context of COVID-19. Although there are currently no data regarding the use of Pioglitazone in patients with COVD-19.

Also dipeptidyl peptidase-4 inhibitors, through the mTOR pathway, appear to restore insulin secretion by improving autophagy in mice induced by a high-fat diet [74]. In fact, the study of Limei Liu et al. showed that phosphorylation of the mTOR pathway stimulated insulin secretion in obese mice [74]. Therefore, even this drug, due to its mechanism of action, could represent a resource in the context of COVID-19. However, there is currently a lack of data regarding the use of DPP-4 in patients with COVID-19.

Others anti-diabetic drugs, such as peroxisome proliferator-activated receptor γ (PPARγ) activator and glucagon-like peptide 1 receptor (GLP-1R) agonist, have been shown to upregulate ACE2 in animal models, which may increase the risk of SARS-CoV-2 infection [75].

Although it is well known that in addition to metformin, other antidiabetic drugs also act on the mTOR pathway, however little is known about their potential role in COVID-19 than metformin.

6. Conclusion

There is still a lot to learn about the etiopathogenetic mechanisms underlying COVID-19 in patients with diabetes. What emerges from this review is that the etiopathogenetic mechanisms that characterize diabetes in this category of patients, seem to favor the dysregulated inflammatory process underlying COVID-19 and, moreover, this would also partly explain the worst outcome observed in such patient category. The mTOR pathway would seem to play a key role. From the data available, it appears that the activation and stimulation of this pathway instigates/triggers an inflammatory process that is already dysregulated, while its inhibition could regulate this dysregulated inflammatory process. However, much remains to be clarified about the mechanisms of the mTOR pathway and its role in COVID-19. The action of metformin and other antidiabetic drugs such as pioglitazone, DPP-4 inhibitors, GLP-1 agonists and SGLT2 inhibitors, could have an important impact on the evolution of COVID-19 through their action on the mTOR pathway. However, while for metformin there are a series of data regarding its use in patients with COVID-19, on the other hand, for the other antidiabetic drugs, data regarding their use in patients with COVID-19 are almost absent. This review has the purpose of being able to represent a starting point and a stimulus to deepen this topic, in order to understand the etiopathogenesis underlying COVID-19 in diabetic patients and in order to be able to find new weapons to deal with this disease.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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