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Research Article

Autoimmune Disease after Trauma could form the Hypothesis of a 2nd Controlled Hit against SARS-Cov-2

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Abstract

The Autoimmune Diseases (ADs) synthesize a group of more than 70 ADs as Multiple Sclerosis (MS) and Psoriasis (PS). The immune reaction in trauma is mainly represented by the Systemic Inflammatory Response Syndrome (SIRS) and the Compensatory Anti-Inflammatory Response Syndrome (CARS) releasing diverse cytokines as IL-6. The immune system seems to be responsible for the ADs, the presence of Ads following the trauma and the infection caused also from SARS-CoV-2. The common dominator of these situations seems to be the IL-6. Taking into account the knowledge on the immune system, the hypothesis of a 2nd controlled hit could be useful in the battle against SARS-CoV-2.

Keywords: SARS-CoV-2; Autoimmune diseases; Antibodies; Multiple sclerosis

Introduction

The immune system in the one hand is necessary for the survival of the human being but on the other it seems to be responsible for the Autoimmune Diseases (ADs). The latter ones synthesize a group of more than 70 ADs as Multiple Sclerosis (MS), Psoriasis (PS), Rheumatoid Arthritis (RA), Lupus Erythematosus (LE), autoimmune thyroiditis (i.e., Hashimoto), etc... [1]. These diseases are characterized by a specific response of the immune system against different areas of body sharing similar mechanisms. Autoimmune diseases could appear after a failure of tolerance to self-antigens with produce of auto antibodies or they could happen after stress or trauma [2,3].

Nowadays effective control of hemorrhage saves the life of the injured after trauma as it happens during a Road Traffic Collision (RTC). So, for a large group of people involved in RTC the immune response to trauma is potentially available for scientific investigation and observation when the massive hemorrhage following an RTC is under control. The immune reaction is mainly represented by the Systemic Inflammatory Response Syndrome (SIRS) and the Compensatory Anti-Inflammatory Response Syndrome (CARS) [4]. So, the immune reaction could support the hypothesis of a defense against any external aggressive factor like viruses in human body.

The immune reaction representing by SIRS and CARS are following an injury (first hit) in the above sequel or in a simultaneously mode as they are overlapping in their transition and release diverse cytokines as interleukins [5,6]. One of these cytokines is the IL-6. It seems to be responsible for the connection between the immune system and the axis of Hypothalamus-Pituitary-Adrenocortical (HPA). Recently there has been evidence of a correlation between autoimmune diseases as MS and PS with the HPA axis [7-9]. Therefore, it seems to be a connection of the immune response after trauma with the autoimmune diseases. This is going to be based on a comprehensible and logical analysis of the current knowledge particularly related to the IL-6. This connection will propose and highlight the pathway to treat the Ads. So, the hypothesis of this study is based on the above knowledge of the immune reaction and of ADs and place the question if the immune reaction could serve as a treatment against viruses like SARS-CoV-2 in a diverse mode of a second controlled hit (the first hit is the injury or the infection) [10-13].

Materials and Methods

Similar mechanisms seem to be responsible for a variety of ADs. According to a notion the etiology of ADs is supported by three elements that form a stable base to analyze and understand the nature of these diseases. These elements are referred to genes, auto antibodies and environment. There are studies present the association of several genetic loci with ADs and of specific clinical outcomes. At the same time other studies focus on the occurrence of auto antibodies as a common feature of most ADs. Recently the role of environment in the development of ADs is under review [14,15]. Environment is referred to external factors that could affect the presence of ADs as smoking, virus-germ (i.e., Coronavirus), trauma etc. [16]. Looking carefully studies referred to ADs and combined the information conducted from them, it is presumed that the common dominator of these 3 factors (genes, auto antibodies, environment) related to ADs are the cytokines [11,12].

Among them cytokine IL-6 seems to play a strong role to the immune response of body also after trauma. It is detected in blood after trauma for an extended period, and this is probably one more reason that has taken much attention for investigation unlike the other cytokines [17]. In addition, there are receptors of the IL-6 to

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hypothalamus that consequently affect the axis of HPA. Recently one prospective Harvard study has correlated the LE with trauma and Post-Traumatic Stress Disorder (PTSD). In this study more than 55000 women were recruited and it was found that there was a statistical connection between PTSD following a trauma event as RTC or sexual assault with an autoimmune disease that was the LE [18]. In another study it has been observed that after a pelvic fracture there is a possibility of the development of an autoimmune disease as MS and PS [19].

It is widely known that after a trauma there is an immune response of the body that suffered the injury. This response is translated to SIRS and CARS. During the process of these syndromes diverse cytokines are recruiting just like IL-6 which is playing a pro and anti-inflammatory role. The release of these proteins happened from T-lymphocyte after their stimulation from the Damage-Associated Molecular Patterns (DAMPs). Then cytokines activate B-lymphocyte to release the self-antibodies. The immune response to trauma depends on factors as the severity of the initial injury, the genome, the physical status and the psychology of the patient as well as of the interventions that have taken place to overturn the injury itself [5,6]. Except from T-lymphocyte, IL-6 can be released from pelvic or adipose stem cells [20]. Furthermore, a receptor of IL-6 has also been found on the hypothalamus as a recent study has shown [21]. This is probably the reason that anti-interleukin-6 agent is used for the treatment of RA [22]. Evidence also show that this agent (anti IL-6) has been effective for the treatment of a patient suffered at the same time from RA and MS [23]. Lately there is evidence of a correlation between MS and PS with HPA axis [24]. At the same time there are other studies correlating MS with IL-6 [25]. Considering that ADs share similar mechanisms, the recent observations on HPA axis and ADs and the fact that in Hashimoto disease the axis of HPA play a well-known significant role, we could hypothesize that this axis is probably the connection key of Ads [26]. It seems that the common denominator of trauma, Ads and any inflammation (i.e., Coronavirus) is the IL-6 and its combined properties [11,12,15,17,18,22,27].

A pathway for the treatment of an autoimmune disease which starts from trauma and finishes at HPA could be drawn in a linear shape which includes two horizontal arrows between trauma, the IL-6 and the HPA axis and three vertical arrows. The management of ADs should focus in any of these three steps. Consequently, every vertical arrow could demonstrate the potential target to prevent or treat ADs (Figure 1).

The first arrow represents the prevention of trauma. It is known that an RTA is not an accidentally fact, but it is a series of facts that lead to the event of the accident. For example, when the driver is out of seat belt or he is speaking to a mobile device during driving the possibility to sustain an injury increases. Learning to avoid the above actions is a preventative measure of injury and of a possible AD [28,29].

The second arrow is representing the effort to block the IL-6 or not to allow surplus release of it after the trauma. Experimental study on mice has shown that suppression of IL-6 signaling could be a viable strategy to limit the consequences of sustained inflammation following a severe injury. In this study, C57BL/6 mice were treated with anti-mouse-IL-6 monoclonal (anti-IL-6 mAb) after injury and prior to resuscitation. The results of the study support the notion that transient and delayed suppression of IL-6 signaling could be a beneficial therapeutic goal in blunt trauma associated with hemorrhagic shock when IL-6 is overproduced [30].

The third arrow shows the effort to block the receptors of the IL-6 as the IL-6R and the gp130 in hypothalamus. There are two unique and similar pathways that can activate the receptors of the IL-6, the classical and the trans-signaling especially through the gp130 receptor. A study has shown that repeated stress to rats provokes changes in the IL-6 and the IL-6R mRNAs in the brain and hypothalamus [30,31]. Taking this into account and the fact that there is a microglial IL-6 hypothalamic expression it is crucial to decrease the level of the IL-6 using diverse blockers [32]. So, a humanized anti-IL-6 receptor (IL-6R) antibody is used for the treatment of an autoimmune disease as it happens in rheumatoid arthritis [32].

If the above blocking measures are going to fail, another mechanism well-known as second hit after trauma could be tested. This theory of the second hit could serve also as defense against any attack from diverse virus as Coronavirus. It is possible that this second hit could serve as a source of IL-6 with anti-inflammatory use. But in this stage, it has to be a controlled and promptly treated second hit which means it will be under supervision for the production of anti-inflammatory cytokines as IL-6 [17]. All the above information could be described as a salvage triangle where its three peaks represent the trauma, the IL-6 and HPA axis respectively and in the center of the triangle is the second controlled hit (2nd ch) (Figure 2). In reality the above three measures are used to block the pro-inflammatory action of IL-6 and suppress its functional, immediately after and during the descent of the SIRS (Systemic Inflammatory Response Syndrome) curve the second controlled hit is going to be provoked and produce IL-6 with anti-inflammatory action (Figure 3). This schematic representation in figure three is based on various studies and is a combination of the current knowledge on the behavior of SIRS and CARS [5,6]. Therefore, Figure 3 shows that when the first hit takes place (1st hit) CARS starts the same time with SIRS but in a slower and reverse trajectory. Around the fifth day (d:5) the second controlled hit (2nd chit) could possibly activate the anti-inflammatory action. This is the time period when a surgery is following after the damage control orthopaedic (DCO) [33].

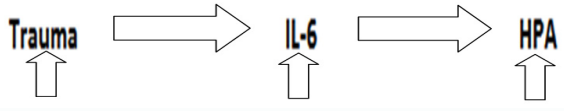

Figure 1: The multilateral pathway of treatment (IL-6; interleukin-6, HPA; hypothalamus-pituitary-adrenocortical).

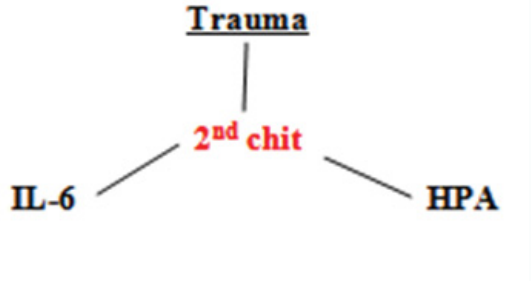

Figure 2: The triangle of salvage (IL-6; interleukin-6, HPA; hypothalamus-pituitary-adrenocortical, 2nd chit; second controlled hit).

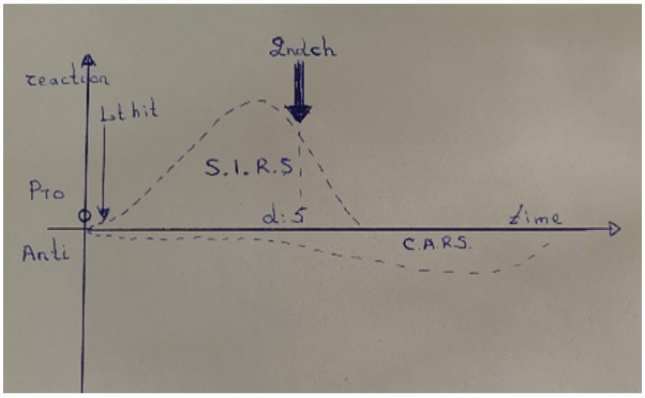

Figure 3: Schematic presentation of the immune response following a traumatic event as inflammation by virus. Reaction: vertical axis, pro: pro-inflammatory, anti: anti-inflammatory reaction. Time in days: horizontal axis, d:5: day five. SIRS, the curve over the horizontal axis: systemic inflammatory response syndrome. CARS, the curve under the horizontal axis: compensatory anti-inflammatory response syndrome. 1st hit is the slim arrow. 2ndchit: second controlled hit is the dense arrow.

Discussion

This study has examined the influence of the IL-6 to autoimmune diseases as well as a hypothetic theory of a second controlled hit. Interleukin-6 is a proinflammatory cytokine that was first identified as a B-cell stimulator factor [34]. In fact, the IL-6 is a prototypical cytokine which is pleiotropic. It is produced mainly by macrophages in response to Damage-Associated Molecular Patterns (DAMPs), and performs a protective function by removing infectious agents and healing damaged tissue through immune responses. Persistent production of IL-6 through mostly unknown mechanisms leads to the development of various chronic immune-mediated diseases as autoimmune diseases and even cancers [35].

The IL-6 seems to have a pro-inflammatory role as well as an anti-inflammatory effect. The promotion of insulin resistance and some pro-atherogenic actions are considered negative. The promotion of macrophage alternative activation, the atheroprotective action and insulin sensitizing effect are considered positive [36]. That happens probably because the production of the IL-6 and its role at any time of injury depends on the type of activation, classical or tran-signaling as a study has shown [37]. The current knowledge is not clear about the properties of IL-6 but it seems that after the second hit in the schematic representations of the curves SIRS and CARS the properties of the IL-6 are changing from pro to anti-inflammatory action [6].

When the IL-6 is synthesized transiently, it promptly participates in the host defense against environmental stress such as infection and injury and at the same time provides a warning signal by triggering a broad spectrum of biological events. However, the dysregulated persistent IL-6 production could be responsible for the appearance of various autoimmune, chronic inflammatory diseases and even cancers. The reason why such dysregulated continuous IL-6 production is induced remains to be understood. Clinical trials of tocilizumab as a humanized anti-IL-6 receptor (IL-6R) monoclonal antibody have demonstrated its outstanding efficacy for rheumatoid arthritis, systemic juvenile idiopathic arthritis systemic juvenile idiopathic arthritis, and Castleman's disease [12]. Tocilizumab as an IL-6R was developed on the basis of a comprehensive view of the IL-6-mediated signaling system [38].

There are receptors of IL-6 on hypothalamus as one study has shown [39]. This study pointed out that IL-6 through gp130 and IL-6 hypothalamus receptors contributes to depression and affects HPA axis. Another study has investigated the relationship among cachexia, multiple sclerosis and HPA axis. It seems that systemic inflammation is a key component of cachexia and is associated with elevated serum levels of inflammatory cytokines such as TNF-α, IL-6, and IL-1β, similar to MS [40]. Also, several studies that have examined the hypothalamic dysfunction in MS show dysfunctional secretion of hypothalamic peptides and hormones in MS patients. Furthermore, there are other authors who investigated whether the activity of the Hypothalamic-Pituitary-Adrenal (HPA) axis was associated with psoriasis. These findings indicated that HPA dysfunction may also be present in psoriasis. Alternatively regarding ADs there is a general consensus that a common genetic background predisposing to autoimmunity (genetics) and at the same time a genetic influence on the IL-6 level [8,9,41].

Furthermore, there is evidence supporting a significant role of the IL-6 during viral infections as one study has shown [16]. In this study two different hypotheses have been considered to explain the change in IL-6 production during the immune response to viral infection: (i) the increased ability of some viral strains to regulate the production of IL-6 and (ii) polymorphisms in the IL-6 gene promoter stimulating over expression of IL-6 during the immune response. The pleiotropic action of the IL-6 function might stem from different viral stimuli activating defence host mechanisms [42]. In this point the theory of the second controlled hit could be examined. A host which is infected by various viruses for example, flu or Coronavirus is going to develop cytokines as the IL-6 with probably pro-inflammatory action. This is the time to suppress the immune system and provoke the second controlled hit. This theory is supported by another study related to lung injury. The authors demonstrated the role of IL-6 in acute lung injury, with a paradoxical protective action against vascular leakage, and suggested that the influence of the IL-6 on the inflammatory cells may represent the primary mechanism by which the IL-6 contributes to acute lung injury. The authors of this study conclude that further research will have to be performed to clarify the mechanisms of the action of the IL-6 in inflammation associated with ARDS. So, a dual-injury model exhibits utility in evaluating the pleiotropic effects of the IL-6 in ARDS on inflammatory cells and lung endothelium as a research has shown [43].

But still the question remains about the diverse action of the IL-6 as pro or anti-inflammatory agent. In this point there is another study which tries to clarify the pleiotropic action of the IL-6. One possibility is that IL-6 plays a pro-inflammatory action in acute inflammation, but also exerts immunosuppressive/anti-inflammatory actions when expressed at lower levels. Another option is that the IL-6 exerts opposite roles in different cell types. Indeed, this has already been suggested to account for the conflicting effects of the IL-6 in insulin signaling, since the IL-6 seems to promote insulin resistance in hepatocytes and endothelial cells but increases insulin sensitivity in skeletal muscle. This could be related to differences in the expression of intracellular mediators of IL-6 signaling, as it has been shown that ablation of one of these mediators (SOCS3) shifts the cellular effects of IL-6 from pro-inflammatory to anti-inflammatory in macrophage. Finally, the complex actions of IL-6 may be linked to the different manners by which this cytokine signals at the plasma membrane. The IL-6-induced cell signaling can be classified as either classic or

trans-signaling, and these two variants can lead to markedly different cellular responses [36,37, 41,42]. So, the controlled second hit could focus on areas with skeletal muscles as it seems that the production of the IL-6 plays anti-inflammatory role. However, in this study the pathway in which manner the second hit will have a positive role in the inflammation is not clear [43].

The answer could be given by the Mesenchymal Stromal Cells (MSCs). These have been identified in essentially all the tissues of the human body, with a major source of cells for clinical uses in bone marrow (BM-MSC), adipose Tissue (AT-MSC), and perinatal tissues as placenta or umbilical cord Wharton jelly (WJ-MSC) [44]. These agents are assumed to be promising both for regenerative medicine and cell therapy for autoimmune disorders. Under the influence of some factors, mesenchymal stem cells secrete cytokines which induce suppression of the immune response. Studies on the secreted cytokines and on suppressive mechanisms would create possibilities for efficient application of MSCs on therapeutic protocols for treatment of autoimmune diseases. When MSCs were tested for 120 cytokines at mRNA and protein levels, it was established that the IL-6 has the highest expression and the conclusion was made that the IL-6 was the basic cytokine responsible for the immunoregulatory effects of MSCs. Also, the IL-6 stimulates the secretion of IL-10 which is a pleiotropic cytokine (stem cells). Recent studies have discovered a transient existence of MSCs in the deep veins around trauma because these agents are recruited to damaged areas *via* several chemo attractant pathways where they function as "actors" in the healing process [20,45,46].

Conclusion

This study is based mostly on the opinion of the author, which is a limitation; it highlights the existed treatment of autoimmune diseases as rheumatoid arthritis using the antibody IL-6R called Tocilizumab. It is certain that more studies will need to take place in order to establish the management of Ads, focus in the HPA axis and relate the trauma with Abs and the IL-6. Furthermore, this study demonstrates the correlation supported by scientific knowledge of the IL-6, the immune system and the infections derived from virus such as SARS-CoV-2. Taking into account the scheme of SIRS and CARS curves as several studies have shown, the time of the second hit is the time where the response of the immune system seems to turns-over from the pro-inflammation to anti-inflammation status. Also, it seems that SCs are recruited to the injury area with anti-inflammatory action as they secret cytokines. All these probably contribute to the anti-inflammatory response. There is also evidence that the IL-6 plays an anti-inflammatory role in the skeletal muscles. On the other hand, a recent study demonstrates the fact that when a fracture, as a second uncontrolled hit, is following an infection COVID-19 seems to burden the physical status of the subject [47]. But in our study seems that when the second hit is under controlled and at the same time is following a generalized suppression of the IL-6 could probably improve the life of the patient suffered from severe side effects, as respiratory, caused by covid-19. It is certain that this hypothesis needs preclinical studies in animals or clinical studies to be proven correct.

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