

Mechanisms of over-activated innate immune system regulation in autoimmune and neurodegenerative disorders

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Abstract: Reactions of innate immunity include phagocytosis, the production and activity of cytokines, chemokines, and adhesion molecules, the killing of infected or changed cells by NK cells and complement activated by natural lectins, and the cytokine-dependent resistance of leukocytes to viral infection. All these mechanisms maintain innate immunity. Deficiency in this immunity is sometimes accompanied by frequent bacterial and viral infections. When innate immunity is permanently stimulated and the intensity of the reactions is stronger, these mechanisms may be directed against the host and subsequently stimulate acquired immunity (antibody and cellular immunity). A higher production of cytokines, oxidative stress, and a high production of NO accompany autoimmunity and neurodegeneration. The possible participation of innate immune receptors, cytokines, and other factors in the development of autoimmune and neurodegenerative diseases is discussed. The importance and possible role of blood-derived microglial cells in the prevention or elimination of amyloid deposits and plaque formation is described. A possible regulatory system, based on the presence of suppressors of cytokine signaling (SOCS), receptors of the Tyro-3 family, adenosine and adenosine phosphates, and IL-10, is reviewed. This review presents the mechanisms involved in the control of the innate immune response by microglia in the development of neurodegenerative disorders.

Keywords: innate immune reactions, deficiency of innate immunity, over-stimulation, regulation system, neurodegenerative disorders

Introduction

The mechanisms of protection against infection are mediated by two general systems: innate and adaptive immunity (Blach-Olszewska 2005). They differ in their detection systems (their receptors and the molecular structures of the pathogens detected), the cells engaged, and their functions. These two systems cooperate very closely. Receptors of the innate system include Toll-like receptors (TLRs), stimulating receptors of natural killer cells (eg, NKG2D), and scavenger receptors (SRs). Moreover, natural lectins, such as mannose-binding lectin (MBL), collectins, and ficolins play roles as innate immunity receptors. All the receptors recognize pathogen-associated molecular patterns (PAMPs) as well as endogenous molecules (Johnson et al 2003).

Reactions of the innate immune system of vertebrates include:

- phagocytosis of cells opsonized by natural lectins, with intracellular pathogen killing (oxygen burst) and efficient removal of cellular debris (Lu et al 2002),
- the production and activity of cytokines, chemokines, adhesion molecules, and other agents such as defensins and NO (Blach-Olszewska 2005; Chang et al 2005),
- the killing of infected or changed cells by natural killers (NKs) or by the alternative or lectin-activated complement system (Carayannopoulos and Yokoyama 2004; Ferlazzo and Münz 2004; Fujita et al 2004),

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- the innate resistance of leukocytes and other cells *ex vivo* to viral infections (Orzechowska et al 2003; Paradowska et al 1996; Zaczyńska et al 1995).

In our laboratory, leukocyte resistance directed against viruses belonging to different taxonomic groups was found. It was reduced by addition of anti-IFNs and anti-TNF α antibody before viral infection and was also diminished *in vitro* in 1- to 5-day cell cultures. This resistance is thus one of the mechanisms of innate antiviral immunity. A test based on the resistance of leukocytes to viral infection was developed in our laboratory (Orzechowska et al 2003). The test is based on the kinetics of vesicular stomatitis virus (VSV) replication in freshly isolated peripheral blood leukocytes. When the titer of VSV reaches 0–1 log TCID₅₀ innate immunity is good, when the titer is low (2–3 log) innate immunity is partial, and a high titer (>4 log) indicates low or deficient immunity.

The correct functioning of such reactions as phagocytosis, with successful removal of pathogens and pathogen-infected cells or apoptotic bodies, a reasonable production of cytokines, cytokine-dependent leukocyte resistance to infections, and the indispensable killing of pathogen-infected cells by NKs and complement guarantee homeostasis in the organism. Sometimes, however, deficient innate immunity is observed.

Deficient innate immunity

A deficiency in innate immunity might be an inheritable disorder. Toll-like or cytokine receptor signaling are involved in this pathology (Ku et al 2005). Mutations of genes for signaling proteins (IRAK4, MEMO, I κ B α) are responsible for primary immunodeficiency. Lower antiviral nonspecific immunity of human leukocytes was observed in elderly blood donors' leukocytes by Rybka and colleagues (2003). A deficiency in the innate antiviral immunity of leukocytes is usually accompanied by remarkable sensitivity to viral and other infections and cancer diseases. Leukocytes of patients with frequent infections of the upper respiratory system or frequent incidences of herpes labialis showed deficiency in innate immunity (Orzechowska et al 2003). The degree of innate immunity also influences the course of HCV infection (Unpublished data) and the progress of acute leukemia (Blach-Olszewska et al 2005). We found that the intensity of innate immunity is a prognostic factor for acute leukemia. All leukemic patients with complete innate immunity of leukocytes at diagnosis achieved long-lasting complete remission after chemotherapy and are now in good condition. In contrast, there was no remission in patients with a deficiency in innate immunity and all of them died 3–25 months after diagnosis.

However, not only inefficiency of the innate immune system is dangerous, but also its over-stimulation.

Over-stimulated innate immunity

Over-stimulation of the innate system with the engagement of TLR receptors, a higher production of cytokines, and a stronger killing of cells is supposed to be the reason for the extreme cell decline in, for example, virally infected liver or alcohol-related liver disease. The cachexia observed in AIDS patients is also probably connected with over-stimulation of the innate immune reaction by HIV (especially HIV gp120 protein) and other opportunistic infections (our study showed extremely high resistance to VSV in leukocytes of AIDS patients). Over-activation of the innate immune system seems to be involved in the development of autoaggression. As reviewed by Rifkin and colleagues (2005), there is an increasing number of studies on the participation of innate immunity TLRs in the immune response in autoimmune diseases. Self molecules, largely originating from apoptotic bodies that have been altered in some way from their native state or which have accumulated in nonphysiological sites or amounts, are recognized by TLRs or by NKG2D present on NK cells. Defective or delayed clearance of these bodies might result in the release of autoantigens. According to Rifkin and colleagues (2005) this defect may be a primary effective cause of the development of autoimmunity. The proper production of cytokines, perhaps a constitutive production of interferons (IFNs) or TNF α by specialized cells, participates in maintaining innate immunity; however, when excessively produced, the cytokines may be directed against the host. Among the most important cytokines in innate immunity seem to be IFNs, cytokines of the TNF superfamily, and some interleukins. However, Baccala and colleagues (2005) consider IFNs type I and type II as the most pathogenic effectors in autoimmunity. According to the authors, these IFNs are the most pleiotropic molecules among the cytokines and primarily appear following adaptive immune responses through:

- the up-regulation of MHC and costimulatory molecules,
- magnification of IFN production and signaling by cross-talk among themselves,
- their synergistic or antagonistic effects on other cytokines,
- the direct or indirect initiation of transcription of immunologically relevant genes.

A typical example of an autoimmune disease is myasthenia gravis. The contribution of autoantibodies directed against the acetylcholine receptor (AChR) present in the blood of most patients was considered to play a role in the

development of this disease. Neutralization of the receptor impairs the synaptic transmission of nerve signals and leads to muscle weakness. The effect of cytokines on acetylcholine receptor expression was studied by Poëa-Guyon et al (2005), who found that AchR transcripts are up-regulated by IFN γ , and even the effect of IFN γ is more pronounced in the presence of TNF α . Up-regulated AchR, according to the authors, may initiate myasthenia gravis. By the effect of cytokines on AchR expression they proved the contributions of IFN γ and TNF α in the initiation of the autoimmune anti-AchR response.

An over-activated innate immune system may participate not only in the development of autoimmunity, but may also play a role in the pathogenesis of neurodegenerative diseases (Lehnard et al 2003; Jung et al 2005; Tanga et al 2005; Moisse and Strong 2006), lung fibrosis (Strieter and Keane 2004), inflammatory bowel disease (Elson et al 2005), and in the remodeling process in asthma (Cembrzyńska-Nowak et al 2005). In most neurodegenerative disorders, including Parkinson's disease, Alzheimer's disease, multiple sclerosis, and AIDS dementia, massive neuronal cell death occurs as a consequence of an anarchic, uncontrolled inflammatory response (Godbout et al 2005; Walker et al 2006). Additionally, defective clearance of amyloid- β by macrophages of Alzheimer's disease patients is observed (Fiala et al 2006). In the CNS, microglia play the role of resident phagocytic cells. Their physiological function is protecting neurons from invading microorganisms as well as removing products of cell degradation (Blais and Rivest 2003; Stolzing and Grune 2004; Simard et al 2006). A critical role in this process is played by a receptor of the innate immune system, TLR4, and by cytokines, especially IFN β (Jung et al 2005). However, over-activated innate immunity may also participate in the development of neurodegenerative diseases (Simard and Rivest 2005). Furthermore, blood-derived cells enter the brain in Alzheimer's disease (AD) and in mouse models of the disease at increased frequencies (Togo et al 2002; Malm et al 2005). Apart from this characteristic neuropathology and the accompanying neurodegeneration, it has become clear that local immune responses involving glial cells and the complement system are activated in the AD brain as well (Wyss-Coray 2006). When the microglia are permanently activated, for example by amyloid- β in AD or by the HIV protein gp120 in AIDS dementia (Rogers and Lue 2001; Townsend et al 2005), they cause inflammation by the production of a variety of inflammatory mediators. Through the activated TLR4-dependent pathway, the microglia product NO causes the degeneration of neurons. The neurodegenerative activity

associated with NO production by microglia was found by Liberatore and colleagues (1999) in a murine model of Parkinson's disease. According to Bate and colleagues (2006), prostaglandin D also mediates neuronal damage.

Regulation of innate immunity

As both deficiency and over-activity of the innate immune system could be detrimental, a very effective regulatory system should exist in an organism. Up to now, possible mechanisms of upregulation have been partially described. Some constitutively expressed cytokines, such as the IFNs, and TNF α , are the endogenous stimulators of natural immunity (Paradowska et al 1996; Orzechowska et al 2003). Innate immunity is stimulated also by a neuropeptide known as substance P (SP). Lighvani and colleagues (2005), in studies on corneal resistance to *Pseudomonas aeruginosa* infection, showed that SP has a stimulatory effect on NK cell-induced IFN γ production through interaction with its receptor, NK-1R. SP is present in lymphocytes and the CNS and plays an important role in dendritic cell (DC) and macrophage function. When innate immunity is over-stimulated, the reduction of riotous reactions should be regulated by control mechanisms. Possible effectors engaged in the control of innate immunity include:

- suppressors of cytokine signaling (SOCSs),
- the Tyro-3 family of receptors,
- adenosine and adenosine phosphates,
- the cytokines IL-10 and TGF β ,
- soluble TLRs or cytokine-receptors.

Additionally, regulation on cell contact, ie, of NKs and DCs, is postulated.

Many cytokines, eg, interferons, members of the TNF family, and the interleukins (IL-12, IL-18), take part in maintaining the innate immune system, so suppressors of cytokine signaling (SOCSs) may play an important role in controlling innate immunity (Elliott and Johnston 2004; Yoshimura 2005). These are members of a family of intracellular proteins, and several of them have emerged as key physiological regulators of cytokine-mediated homeostasis. In the family of SOCSs are eight suppressors induced on cytokine stimulation. They then block further cytokine signaling. Signaling intermediates (JAK, STAT, or the intracellular receptor domain) are degraded next (Elliott and Johnston 2004). Takase and colleagues (2005) suggest that SOCS 5, which is constitutively expressed in the retina, may have a neuroprotective function, while the other cytokine-induced SOCSs may be involved in the negative regulation of inflammatory cytokines during autoimmune uveitis.

Several authors (Kovarik et al 2005; Stark and Cross 2006) found that SOCS-1 and SOCS-3 are induced by cytokines such as IFN γ and IL-6. It is known that the cytokine level is up-regulated during experimental autoimmune encephalomyelitis (EAE). Autoimmune process could be regulated by both molecules (SOCS-1 and SOCS-2). SOCSs not only influence cytokine and growth hormone signaling, but also the signaling pathway initiated by the reaction of a TLR with PAMP or an endogenous molecule. According to Mansell and colleagues (2006), SOCS-1 negatively regulates TLR signaling by mediating the degradation of the adapter protein Mal. This protein is involved in signaling via TLR-2 and TLR-4. Because of their obvious biological importance, the SOCS proteins have been the subject of intense investigation, including the development of strategies to utilize these proteins to control cytokine-induced JAK/STAT signal transduction for therapeutic purposes.

The cytokines IL-10 and TGF β are known inhibitors of innate and adaptive immunity. Both directly affect macrophages; moreover, IL-10 indirectly influences Th1 and NK cells. Lang and colleagues (2002) studied the total effect of IL-10 on the transcriptional response induced in LPS-activated macrophages. They found that TNF and several other cytokines and chemokines are considerably reduced in *in vitro* macrophage cultures and *in vivo* models where mice were challenged with TLR agonists. Moreover, they also found that IL-10 up-regulated the expression of the *socs-3* gene. It is known that the SOCS-3 molecule blocks intracellular IFN γ and IL-6 signaling. The results of Qasimi and colleagues (2005) indicate that SOCS-3 is an important mediator of IL-10 inhibition of macrophage activation. Another cytokine, transforming growth factor β (TGF β), acts as an autocrine regulator of macrophage function, and this regulation was not observed in TGF β -null mice. TGF β -deficient mice had increased TLR expression and were hypersensitive to endotoxin. TGF β 's regulatory role was confirmed in experiments on mice lacking TGF β , which developed multiorgan inflammation due in part to abnormal innate cell responses.

Tyro-3 is another group of molecules with regulatory activity. Three members of the Tyro-3 receptor group: Tyro3, Axl, and Mer, belong to the tyrosine kinases. According to Lu and Lemke (2001) they are responsible for homeostatic regulation of the immune system. They regulate the function of the innate system by limiting the magnitude and extent of macrophage and dendritic cell activation after an initial immune stimulation. In the absence of this signaling system in TAM mice, macrophages are constitutively activated. In

these mice lacking Tyro-3 receptors, elevated expressions of IL-2R, CD69, Fas, and IFN γ were observed. Tyro-3 kinase receptors play a role in the regulation of cytokine production as well as in phagocytosis and the removal of apoptotic cells (Cohen et al 2002). A remarkable diversity of autoimmune disease symptoms resembling rheumatoid arthritis, systemic lupus erythematosus, and other human autoimmune diseases are observed in mice lacking the *c-mer* membrane tyrosine kinase. Tyro3 receptors are expressed on some cells of the immune (Camenish et al 1999; Scott et al 2001; Cohen et al 2002), reproductive (Wong and Lee 2002; Wang et al 2005), nervous (Prieto et al 2000), and vascular systems. The ligand molecules for these receptors are Gas 6 (growth arrest-specific gene-6) and protein S. Expression of the three receptors was shown to play a role in the developing rat central nervous system by Prieto and colleagues (2000). They were found on Purkinje cells, in granule neurons, and in Bergman glia. They were also detected in cerebellar white matter. Lu and Lemke (2001) noted that mutation of the *mer* gene in humans is associated with retinitis pigmentosa. All the studies indicate that Tyro-3 receptors are involved in the regulation of hyper-activated reactions of the innate immune system.

Adenosine and adenosine phosphates (ADP and ATP) belong to the regulatory mechanisms that limit damage caused by an overly increased immune response. The immunoregulatory effect of ATP on cytokine release from stimulated whole-blood cultures was observed by Swennen and colleagues (2005). Lower production of TNF α and higher IL-10 titer were observed in stimulated cultures treated with ATP. Such an effect was not observed, however, when adenosine was used instead of ATP. The protective effect of ATP against cachexia was confirmed in clinical examination of patients with nonsmall-cell lung cancer (stage IIIB/IV) after regular infusions of ATP. The results showed that treatment of patients with ATP was much better than palliative therapy alone (Agteresh et al 2000). The patients' weight, muscular strength, and quality of life were much better than those of the latter group. Other authors pointed out adenosine as an endogenous regulator of innate immunity because of its negative regulatory role in NF κ B and MAPK signaling. This purine nucleoside suppresses TNF α and IL-12 production (Hasko and Cronstain 2004; Ijon et al 2005; Antonielli et al 2006; Kreckler et al 2006; Lee et al 2006). Similarly to ATP, IL-10 production by macrophages is potentiated by adenosine (Nemeth et al 2005). These results indicate that IL-10 may play a role as one of the mediators of adenosine and ATP inhibitory activity. A purine nucleoside, adenosine is a biologically

active molecule that is formed at sites of metabolic stress associated with hypoxia, ischemia, trauma, or inflammation. Because of this, Hasko and Cronstein (2004) called adenosine a “retaliatory metabolite”. Many of its effects are mediated through one or more of four receptors: A_1 , A_{2A} , A_{2B} , and A_3 , which are coupled with specific G protein. The receptors are expressed on monocytes, macrophages, dendritic cells, glial cells, and neurons (Hasko and Cronstein 2004; Lee et al 2005; Zaidi et al 2006) and participate in adenosine-mediated regulation of immunity and inflammation (Anonielli et al 2006). These receptors, as described by Nemeth and colleagues (2005), are seven-membrane-spanning proteins that couple to heterodimeric G proteins and trigger a variety of intracellular signaling pathways.

In addition to the different mechanisms engaged in controlling innate immunity, soluble receptors may also play a regulatory role. Le Bourder and colleagues (2003) found soluble TLR-2 in human plasma and breast milk and considered its role as a regulatory factor capable of modulating TLR2 signaling. Regulatory activity may also be a result of cell contact. Zitvogel (2002) reviewed that contact between immature DC and NK cells finally results in NK activation and DC maturation. After NK cell activation they start to proliferate and produce $IFN\gamma$. The final result depends on the kinetics of NK activation. When NK cells are numerically dominant over immature DCs, the latter are killed. When the proportions of the cell populations are reversed, DCs undergo maturation and their resistance to NK killing is higher. In this way, both innate and acquired immunity are under the influence of cell-cell contact.

It indeed appears that chronic inflammation may be a major driving force in the most important diseases our time: autoimmune and neurodegenerative disorders, especially AD (Simard and Rivest 2006). Age-related diseases such as Alzheimer’s are “the price we pay” for a life-long active immune system: this system also has the potential to harm us later as its fine tuning becomes compromised. We have much to learn about the innate immune system under these conditions. We need to explore the mechanisms whereby the innate immune system recognizes and targets both self and non self, just as we have investigated these issues in the adaptive immune system. We have every reason to believe that therapies that selectively modulate the functioning of the innate system will prove just as valuable as treatments that intervene with the adaptive immune system.

In conclusion, both a deficiency in and an over-activation of innate immunity lead to health problems. A better understanding of the regulatory mechanisms helps us to

understand the causes of autoimmune or neurodegenerative diseases and to plan therapeutic strategies (Marchetti and Abbracchio 2005).

Innate immunity in neurodegeneration of Alzheimer’s type: A possible therapeutic approach

Over the past twenty years, evidence has been accumulating that there is a chronic inflammatory reaction in areas of the brain affected by Alzheimer’s disease and other types of neurological disorders (eg, ischemia, spinal cord injury, multiple sclerosis, prion diseases, Parkinson’s disease, epilepsy). At present there seems to be no doubt that neuro-immune mechanisms contribute actively to the neurodestructive process located in the senile plaques of the AD brain. The senile plaques of AD patients contain deposits of many immune-reaction soluble factors (Rogers 1995). Among them, complement proteins, from the initial component C1q through the terminal cytotoxic C5b-C9, the complement receptors CR3 and CR4, and complement inhibitors, cytokines and interleukins (TNF-alpha, IL-1, IL-2, IL-6), and acute phase reactants (alpha1-antichymotrypsin and alpha2-macroglobulin) were exclusively localized in AD plaques.

Immune cells are present around senile plaques (Wenk 2003). Staining with a monoclonal antibody specific for activated microglial cells revealed a marked increase in these cells in the rims of senile plaques (Dik et al 2005). It seems to be proved that these cells secrete beta-myloid protein and are responsible for the alternative pathway cleavage of beta-amyloid precursor protein to yield amyloidogenesis fragments in AD senile plaques (Dziedzic 2006). A common feature of AD is the abundance of activated microglia in the proximity of neuritic plaques (Akiyama et al 2000). Activated microglia cells released interleukins 1 and 6, TNF-alfa and complement proteins (McRae et al 1993). They can also be a source of potentially cytotoxic metabolites, including reactive oxygen intermediates and nitric oxide (Walker et al 2006). It was also suggested that microglia produce and release anti-brain-tissue antibodies of the IgG class that recognize different neuronal structures and can activate the complement cascade by the classical pathway (Nagele et al 2004).

The presented above data strongly suggest that autoimmune reactions are present in every case of AD. Therefore, immunosuppression should be the treatment of choice. Such treatment can decrease infiltration of the rims of senile plaques by immune cells and also lead to a diminution in

the release of cytokines and soluble inflammatory factors. Steroids seem to be improper candidates for immunosuppressive therapy of AD, since marked changes in the cytosolic glucocorticoid receptors on peripheral blood mononuclear cells (ie, lymphocytes and monocytes) and disturbances in the hypothalamic-pituitary-adrenal axis have been well documented in the disease (Nijhuis et al 1994). Initial clinical trials involving the treatment of patients with nonsteroidal anti-inflammatory drugs (NSAIDs) prior to the development of AD have been suggested to inhibit the immune response. This might reduce the chance of developing the disease (Yip et al 2005). Some authors, however, suggest that NSAIDs have no effect in patients already suspected of having developed AD (Aisen et al 2003) and that treatment with a COX-2 inhibitor increases the amount of Beta-amyloid in the brain (Kukart et al 2005).

It is obvious that immunosuppressive therapy cannot be prolonged and should be stopped after obtaining the optimal possible improvement of the disease (Gąsiorowski and Leszek 1997). It is well known that classical cytostatic drugs exhibit genotoxic activity, which is the cost paid for their anticancer cytotoxic and cytostatic activities. Therefore it is necessary to look for new immunosuppressors, possibly natural ones, for instance those derived from plants, which display low toxic and genotoxic activities. Several reports have been published on the efficiency of natural immunosuppressive drugs in AD treatment (Anekonda and Redy 2005). We tested a natural product isolated from ovine colostrum, proline-rich polypeptide (PRP) complex, called Colostrinin. The complex showed immunomodulatory properties in mice, rats, and chickens, inducing maturation and differentiation of thymocytes. Colostrinin was found to improve the outcome of AD patients with mild to moderate dementia (Leszek et al 1999, 2002). In this context, the neuroprotective mechanisms of acetylcholinesterase inhibitors (AChE), eg, donepezil or galantamine are very important. Tokatori and colleagues (2006) found that donepezil and galantamine protect cortical neurons against acute glutamate treatment-induced neurotoxicity at steps before, and that tacrine protects at steps after nitric oxide radical formation. On the other hand the neuroprotective effects of donepezil and galantamine, but not tacrine, against neurotoxicity induced by moderate glutamate treatment were mediated through the phosphatidylinositol 3 kinase-Akt pathway.

These findings unveiled the hitherto unknown neuroprotective effects of therapeutic AChE inhibitors and provided valuable insights into its neuroprotective mechanisms. They may very likely form the basis for a novel treatment strategy

against AD. Our experiments suggest that the mechanism of protection by donepezil may be related to histamine signaling through the H1R and H2R receptors. We found that donepezil may restore the proper balance between H1R and H2R expression (Leszek et al 2004). In other experimental models of AD it was shown that such agents as monoamine oxidase type B(MAO-B) inhibitors and dopamine agonists exert a neuroprotective effect at the cellular, neurochemical, and functional levels. It has not, however, been possible to demonstrate an unequivocal neuroprotective of these substances in clinical studies (Gerlach et al 2000).

We hypothesize that an important risk factor of AD is the manifestation of immune aging. Immune aging increases susceptibility to the development of autoaggressive reactions, and several known and supposed etiological factors of AD may direct the elevated autoimmune reactions against brain tissue components. The focal infiltration of brain tissue by immune cells and the concentrations of cytokines, inflammatory factors, and B-amyloid compress neurofibrils and neurons adjacent to senile plaques and thus interfere with their normal neurophysiological functions. Therefore, lowering the deposited mass should lead to marked improvement of neurophysiological functions of neurons and neurofibrils compressed by it. This is possible with the use of immunomodulatory or immunosuppressive drugs.

Summing up, all the data presented above concerning a better understanding of the role of inflammation in the development of many neurodegenerative diseases are, in our opinion, required before we can safely develop therapeutic strategies for preventing neuronal damage. Novel therapeutic approaches must rely on the regulation of endogenous anti-inflammatory pathways, identification of early markers of neuronal deterioration, and a combination treatment involving immune modulation and anti-inflammatory therapies.

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