Neuro-Immune Interactions Focus

The gut–meningeal immune axis: Priming brain defense against the most likely invaders

Rafael Di Marco Barros1, Zachary Fitzpatrick2, and Menna R. Clatworthy1,3,4

The gastrointestinal tract contains trillions of microorganisms that exist symbiotically with the host due to a tolerant, regulatory cell–rich intestinal immune system. However, this intimate relationship with the microbiome inevitably comes with risks, with intestinal organisms being the most common cause of bacteremia. The vasculature of the brain-lining meninges contains fenestrated endothelium, conferring vulnerability to invasion by circulating microbes. We propose that this has evolutionarily led to close links between gut and meningeal immunity, to prime the central nervous system defense against the most likely invaders. This paradigm is exemplified by the dural venous sinus IgA defense system, where the antibody repertoire mirrors that of the gut.

Introduction

The central nervous system (CNS), comprising the brain and spinal cord, is arguably the most important of all organ systems, housing the centers that control respiration and heart rate, movement and sensation, higher thought, and reason. In recent years, there has been an explosion of interest in the immunology of CNS-adjacent tissues such as the meninges, the membranes that cover the outer surface of the CNS (Mastorakos and McGavern, 2019). A number of studies have described the presence of innate and adaptive immune cells in the meninges (Mrdjen et al., 2018; Van Hove et al., 2019), and the importance of defining their number, nature, and function lies in their proximity to the brain and their potential to influence brain cell activity and health in homeostasis and disease (Alves de Lima et al., 2020). Meningeal immune cells respond to CNS-intrinsic perturbations, such as neuroinflammation or neurodegeneration (Da Mesquita et al., 2018; Da Mesquita et al., 2021; Louveau et al., 2018), as well as to CNS-extrinsic challenges, such as systemic infection (Fitzpatrick et al., 2020). The meninges may also provide a site for negative selection of CNS antigen-specific developing B cells (Brioschi et al., 2021; Schaflick et al., 2021; Wang et al., 2021). While the majority of studies profiling the function of meningeal immune cells have focused on responses to CNS pathologies, evolutionarily, immune challenges that come from “without” rather than “within” are more likely to be the selective pressure that has shaped where and how meningeal immune cells act; put another way, diseases like multiple sclerosis or Alzheimer’s disease affect humans at an age when reproduction is completed, whereas viral/bacterial meningitis and encephalitis kill infants and children (GBD 2016 Meningitis Collaborators, 2018), and therefore likely represent a powerful evolutionary force that has shaped meningeal immunity to optimize defense against such pathogens. We propose that this concept lies at the heart of why peripheral organs, particularly the gastrointestinal tract, can, and do, shape meningeal immunity.

The meninges: The peripheral interface of the CNS

The meninges of higher vertebrates are composed of an outer dura mater, a middle arachnoid mater, and an inner pia mater. They lie at the interface between the brain and its surrounding bony box, including the calvarium, the bones that form the internal wall of facial structures, like the air sinuses, and those at the base of the skull. The dura mater, the toughest and thickest of the three layers, lies immediately adjacent to the internal surface of the skull bones and vertebral spinal canal and has large folds that dip between the right and left cerebral and cerebellar hemispheres (falx cerebri and falx/tentorium cerebelli, respectively). The dura has a bone-lining periosteal layer and an inner meningeal-serous layer that separate to accommodate the dural venous sinuses (Fig. 1) around which immune cells congregate (Fitzpatrick et al., 2020; Rustenhoven et al.)
It is notable that blood flows relatively slowly through the dural sinuses and the endothelium is fenestrated (Kilic and Akakin, 2008; Schuchardt et al., 2015), providing ample opportunity for the delivery of immunological information to adjacent immune cells. Immunological cues may derive from the local tissues drained by the dural venous sinuses, and macrophages are closely opposed to blood vessels. The arterial blood supply of the dura comes from the middle meningeal artery, with branches supplying arterial blood to the overlying calvarium and underlying dura, feeding capillary beds that drain into dural veins and ultimately into the dural venous sinus. Diploic veins drain the bone/bone marrow, and emissary veins drain the extra-cranial space into the venous sinuses. Unlike the vascular network of the CNS, which is sealed by endothelial cell tight junctions, the dural vascular bed is fenestrated, enabling blood-borne molecules and immune cells to exit the vasculature. This provides a direct means by which physically distant organs, such as the gut, may communicate with meningeal immune cells, or indeed, a potential route of entry by which systemic immune cells (including those stimulated or educated at a distal site) may enter the dura. The dural immune sinuses also receive immunological information from the CNS as CSF may drain into the sinuses via arachnoid granulations.

Figure 1. **The meninges: The peripheral interface of the CNS.** The meninges are composed of the dura, arachnoid, and pia mater. The dura has a bone-lining periosteal layer and an inner serous/meningeal layer that separate to accommodate the dural venous sinuses. Dural immune cells are concentrated around the wall of the dural venous sinuses, and macrophages are closely opposed to blood vessels. The arterial blood supply of the dura comes from the middle meningeal artery, with branches supplying arterial blood to the overlying calvarium and underlying dura, feeding capillary beds that drain into dural veins and ultimately into the dural venous sinus. Diploic veins drain the bone/bone marrow, and emissary veins drain the extra-cranial space into the venous sinuses. Unlike the vascular network of the CNS, which is sealed by endothelial cell tight junctions, the dural vascular bed is fenestrated, enabling blood-borne molecules and immune cells to exit the vasculature. This provides a direct means by which physically distant organs, such as the gut, may communicate with meningeal immune cells, or indeed, a potential route of entry by which systemic immune cells (including those stimulated or educated at a distal site) may enter the dura. The dural immune sinuses also receive immunological information from the CNS as CSF may drain into the sinuses via arachnoid granulations.
The dura itself mostly derives its arterial blood supply from the middle meningeal artery (a branch of the external carotid artery), which feeds a vascular network that runs between the periosteal dura and skull bone. Some of these branches supply arterial blood to the overlying bone, whereas others give rise to precapillary arterioles that penetrate the dura mater feeding into capillary beds (Roland et al., 1987). Dural veins are similarly arranged into a deep and superficial network, with superficial veins running alongside the meningeal arteries and deep veins forming an irregular network within the dura mater before draining into venous sinuses (Fig. 1). Unlike the vascular network of the CNS, which is sealed by endothelial cell tight junctions, the dural vascular bed is fenestrated (Derk et al., 2021). Consistent with this, intravenous horseradish peroxidase (44 kD) accumulated throughout the dura, but not the cerebral parenchyma, in rodents and monkeys (Balin et al., 1986). Furthermore, endothelial cells from mouse dura mater showed limited expression of Claudin-5 and Occludin, two tight junction components that are highly expressed in mouse brain vascular endothelial cells (Dejana, 2004; Rustenhoven et al., 2021). Endothelial fenestrations have been directly visualized in dural veins using electron microscopy (Nabeshima et al., 1975). Thus, the fenestrations of the dural vascularity expose the dura to blood-borne microbes and provide a direct means by which physically distant organs, such as the gut, may communicate with meningeal immune cells, or indeed, a potential route of entry by which systemic immune cells (including those stimulated or educated at a distal site) may enter the dura.

The arachnoid mater is a thin avascular membrane made up of squamous epithelial cells bound by tight junctions and desmosomes, while the inner pia mater adheres to the surface of the brain (Fig. 1) and forms a selectively permeable barrier between the cerebral parenchyma and the sub-arachnoid space (Alcolado et al., 1988; Hannocks et al., 2018). The sub-arachnoid space contains cerebrospinal fluid (CSF), which constitutively undergoes macromolecular exchange with the intravascular spaces of CNS-penetrating vessels (Iliff et al., 2012; Lun et al., 2018). Antigenic sampling of CSF represents a potential mechanism of CNS immunosurveillance, but there is considerable debate as to the anatomical route(s) through which CSF is drained (see recent review [Proulx, 2021]). Historically, the prevailing view has been that CSF drains directly into the dural venous sinuses via the arachnoid granulations (Proulx, 2021), bringing CNS-derived antigens or immune mediators in close proximity with sinus-adherent immune cells. However, tracer dyes, contrast agents, proteins, and even immune cells injected into sub-arachnoid space, cerebral ventricles, and cerebral parenchyma readily accumulate in deep cervical LN9s (dCLNs; Ahn et al., 2019; Antila et al., 2017; Aspelund et al., 2015; Da Mesquita et al., 2018; Louveau et al., 2018, 2015; Ma et al., 2017). Drainage of CSF into the dCLN may take place via meningeal lymphatic vessels (Aspelund et al., 2015; Da Mesquita et al., 2018; Louveau et al., 2018, 2015) or via extracranial lymphatic vessels (Ahn et al., 2019; Ma et al., 2017; Proulx, 2021). In addition, CSF tracers can accumulate in the parasagittal dura independently of meningeal lymphatic vessels (Ringstad and Eide, 2020; Rustenhoven et al., 2021). Therefore, there are likely multiple pathways for CSF drainage, and it is currently unclear how immune cells in the dCLNs differentiate between antigens derived from CSF versus other head and neck sites.

**Meningeal immune cells occupy areas of need**

Meningeal immune cells in homeostasis are most numerous in the dura mater and have been predominantly profiled by generating single-cell suspensions of mouse dura. Flow and mass cytometry studies, as well as single-cell RNA sequencing, have identified a variety of immune cells, including neutrophils, mast cells, monocytes, macrophages, dendritic cells, innate lymphocytes (particularly natural killer [NK] cells, and groups 2 and 3 innate lymphoid cells [ILCs]), γδ T cells, NK T cells, CD4 and CD8 T cells, B cells, and plasma cells (Korin et al., 2017; Mrdjen et al., 2018; Van Hove et al., 2019). However, some methodological limitations should be borne in mind when interpreting these data: First, it is difficult to exclude contamination of cells from the skull bone marrow, as there are several channels that connect the bone marrow and dura. Second, unless an intravenous anti-CD45 antibody is administered prior to dural harvest, the single-cell suspension obtained will inevitably contain intravascular contaminants as well as dural-resident immune cells, even if animals are perfused. Third, some cells are not well represented in single-cell suspensions as they are more closely intertwined within the structural components of the dura and are not released by standard enzymatic/mechanical digestions.

Imaging-based studies overcome some of these limitations and enable the precise location of cells to be described. Such studies have revealed that the vast majority of the area occupied by the dura is pauci-immune, but immune cells are enriched in specific regions, particularly the walls of the dural venous sinuses (Fig. 1), with ILC2 (Gadani et al., 2017), γδT cells (Ribeiro et al., 2019), B cells, and plasma cells (Fitzpatrick et al., 2020), as well as CD8 and CD4 T cells, NK T cells, and FoxP3+ regulatory T cells (Rustenhoven et al., 2021) noted in the peri-sinus area of the superior sagittal and transverse sinuses. Within the dura, the vascular network is guarded by macrophages (Kierdorf et al., 2019) that may be replaced by monocyte-derived macrophages during intra-cranial viral infection (Rua et al., 2019). These perivascular macrophages cluster along the dural sinuses and the veins that feed into them (Rua et al., 2019; Sato et al., 2021), alongside arterioles (Rustenhoven et al., 2021), and straddle dural nerves (Sato et al., 2021). Dural macrophages are largely non-motile, constitutively survey their surrounding microenvironment by extending and retracting dendrites (Kierdorf et al., 2019), but mobilize to encircle damaged vasculature following traumatic brain injury (Mastorakos et al., 2021). Perisinus macrophages and dendritic cells constitutively sample antigens from the circulation and CSF, evidenced by their uptake of fluorescein-labeled OVA injected intravenously and/or into the cisterna magna (Rustenhoven et al., 2021). Overall, the anatomical position of immune cells in the meninges around blood vessels and dural venous sinuses are tailored to bolster defense in vulnerable barrier areas that interface with the periphery via fenestrated endothelium.
Where do CNS invaders arise?

If neurotropic and leptomeningeal infections have driven the evolution of meningeal immunosurveillance, it is informative to consider the most prevalent CNS pathogens and their site of origin. Such infections account for up to ~4% of global deaths in pediatric populations under 9 years of age (GBD 2016 Meningitis Collaborators, 2018). These infections arise either from local invasion or hematogenous spread. In terms of the former, the meninges provide an important barrier to the extracranial environment, to which the CNS is exposed across the various skull base foramina that accommodate the exit of cranial nerves. This defense system is largely effective, but disruption of meningeal integrity by traumatic skill base fractures (evident by the appearance of a CSF leak) is associated with an elevated risk of acute bacterial meningitis (Ter Horst et al., 2020) and of long-term recurrent bacterial meningitis (Adriani et al., 2007). Similarly, a rare complication of dural puncture is iatrogenic meningitis caused by Viridans-type Streptococci transmitted during instrumentation (Baer, 2006). Meningitis can also develop as a consequence of direct bacterial invasion in the context of severe soft tissue/bone infection in adjacent anatomical structures. Hence, mastoiditis (Barry et al., 2019), orbital cellulitis, and sinusitis (Ziegler et al., 2018) can each be complicated by meningitis. Thus, the meningeal barrier is critical for host CNS defense against local invasion, and when normal anatomy is intact, it is largely effective in achieving this, but disruption in the context of traumatic injury or procedural/surgical interventions can be associated with life-threatening infection.

In addition to defending against local invaders, the meninges must also protect the CNS from infectious challenges that metastasize via the hematogenous route. Such hematogenous spread is thought to account for the majority of community-acquired bacterial meningitis (van de Beek et al., 2021), and given that dural vascular endothelium is fenestrated, it is an area of vulnerability for the CNS, as discussed previously. The underlying microbial causes of meningitis vary with patient demographics, clinical context, and environmental exposure. However, it is notable that the majority of these blood-borne infections are thought to derive from the respiratory tract (van de Beek et al., 2021). Hence, Pneumococcus, Meningococcus, and Haemophilus influenzae B are globally the most common causes of bacterial community-acquired meningitis, and enter the host bloodstream via the respiratory tract mucosa (van de Beek et al., 2021). Gut bacteria do not commonly cause meningitis (Unhanand et al., 1993; van de Beek et al., 2021). Exceptions include Listeria monocytogenes, which can cause severe CNS infection in the immunosuppressed or during pregnancy. Group B Streptococci, Escherichia coli, and Klebsiella pneumoniae can also cause severe meningitis in newborns and infants and are likely introduced orally into the newborn during labor (Pelkonen et al., 2020).

It is notable that if we compare the list of pathogens that commonly cause meningitis in children and adults to those most commonly isolated from blood, there is a disconnect. Aside from neonates, bacteria originating in the gastrointestinal tract are largely well defended by the meninges. For example, in developed countries, patients presenting from the community with bacteremia most frequently present with non-salmonella, gut-derived gram-negative bacilli, such as E. coli, K. pneumoniae, and Pseudomonas aeruginosa, although many of these patients have chronic diseases (diabetes, cancer, organ failure) with associated healthcare exposure (Cross and Levine, 2017; Takeshita et al., 2017). The estimated prevalence of gram-negative bacteremia in the U.K. is 65 per 100,000 for E. coli alone (Public Health England, 2021), whereas the prevalence of gram-negative meningitis is <0.5 per 100,000 (McGill et al., 2018). In developing countries, where there is less health care contact and epidemiology may more faithfully reflect evolutionary bacterial pressures, longitudinal studies (e.g., in Malawi) report non-typhoidal salmonella as a leading cause of bacteremia, with Salmonella typhi emerging in epidemics (Musicha et al., 2017). However, as in developed countries, Streptococcus pneumoniae and Neisseria meningitidis are the most common causes of bacterial meningitis (Brown, 1975), aside from the more recent increase in cryptococcal meningitis in the setting of HIV infection (Gordon et al., 2000). We would contend that the fact that gut-derived bacteria are the major source of bacteremia but do not commonly lead to CNS infections is remarkable. Although this discrepancy may, to some extent, reflect intrinsic differences in virulence factors between distinct species of bacteria, e.g., N. meningitidis, S. pneumoniae, and H. influenzae express IgA proteases (Kilian et al., 1979; Mulks et al., 1982; Mulks et al., 1980), it may also be due to linked immunity between gut and meninges. Evolutionarily, enabling the intestine to educate or influence meningeal immunity is an obvious way to prime CNS defense against the most likely blood invaders.

Gut–meningeal immunity

In considering how meningeal humoral immunity may adapt to the threat of distal mucosal challenge, we recently proposed that the meninges homeostatically recruit intestinal immune cells to defend the walls of the dural venous sinus (Fitzpatrick et al., 2020). Antibody production is at the heart of humoral immune responses, and a function of terminally differentiated B cells termed plasmablasts or plasma cells. The constant region of IgG, comprised exclusively of heavy chain proteins, determines antibody isotype and dictates effector functions. IgA is the predominant antibody isotype produced in intestinal tissue; it exists largely in dimeric form and is often polyreactive such that a single clone can bind multiple microbial species. Luminal IgA can neutralize intestinal pathogens and pathogen-derived toxins, as well as induce enchainment of gut-resident microbes (Bunker et al., 2017; Fagarasan, 2008; Moor et al., 2017).

While assessing the humoral immune landscape in the dura under steady-state conditions, we discovered that, surprisingly, IgA was the dominant Ig isotype expressed in this compartment (Fitzpatrick et al., 2020). A subset of meningeal plasma cells coexpressed joining (j) chain, suggesting that a proportion of these cells may secrete polymeric forms of IgA, akin to intestinal plasma cells. Meningeal IgA+ plasma cells were specifically localized to the walls of the dural venous sinuses and were nearly absent in germ-free animals, with their presence restored by gut (but not skin) recolonization. Peri-sinus IgA+ plasma cells and B cells increased in number following intestinal barrier breach.

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https://doi.org/10.1084/jem.20211520
and B cell receptor sequencing of paired meningeal and intestinal tissue in naive animals, which confirmed a shared repertoire of IgA clones between these geographically distant tissues. Specific deletion of meningeal plasma cells by local application of a proteosome inhibitor led to a reduction in microbial entrapment in the peri-sinus region, enhanced spread into the brain, and increased mortality following intravenous candida challenge. This study revealed a critical role for meningeal IgA in protecting the brain from extrinsic, blood-borne pathogens and demonstrated an important link between humoral immunity in the gut and meninges (Fig. 2). The presence of meningeal IgA plasma cells was further corroborated in a recent study, which also reported an age-associated accumulation of IgG+ and IgM+ B cells and plasma cells (Brioschi et al., 2021). Thus, the dura is a dynamic barrier tissue that changes its composition in the context of systemic perturbations and normal aging.

Previous reports had described gut-derived IgA plasma cells in the CNS parenchyma in experimental autoimmune encephalitis (EAE), a mouse model of multiple sclerosis, but focused on their antibody-independent functions (Rojas et al., 2019). Plasma cell–deficient mice developed an exacerbated clinical phenotype, whereas mice with elevated numbers of IgA+ plasma cells were protected from EAE in an IL-10–dependent manner, suggesting that these cells are important immunoregulators in this context. Moreover, when EAE was induced in mice that had recovered from a previous intestinal rotavirus infection, rotavirus-specific IgA plasma cells were detectable in the CNS parenchyma, although the meninges were not examined in this study (Rojas et al., 2019). An anti-inflammatory role for B cells in EAE has long been noted, with B cell–deficient mice lacking surface IgM expression (µ-MT mice) demonstrating delayed recovery from EAE (Wolf et al., 1996), and B cell depletion may both improve or exacerbate EAE, depending on the timing of administration (Matsushita et al., 2008). We recently showed that meningeal B cells may have anti-inflammatory functions in homeostasis and in the context of psychological stress, with CD19–deficient mice demonstrating meningeal myeloid cell activation in homeostasis and a more anxious phenotype, as well as increased expression of IFN-γ– and IFN-α–response genes in the dura following chronic social defeat, compared with controls (Lynall et al., 2021). Therefore, the intestinal education of humoral immunity may have two beneficial effects for CNS defense: producing cells with B cell receptor affinity matured to recognize the likeliest source of blood-borne bacteria and those with an immunoregulatory cytokine profile that can limit CNS inflammation (Fig. 2).

There is also evidence to suggest that other immune cells, beyond B cells and plasma cells, may be recruited from the gut to the CNS in response to a CNS-intrinsic challenge. In a mouse model of stroke, intestinal photoconversion was used to trace the migration of B and T cells from the gut to the meninges (Benakis et al., 2016). While B cells appeared to home to the meninges and the deep and the superficial CLNs, T cells preferentially homed to the meninges. Similarly, a study of meningeal NK cells and their role in regulating a key subset of astrocytes during EAE, utilized intestinal photoconversion to show evidence of NK cell migration from the gut to the meninges (Sanmarco et al., 2021). NK cell migration was lower in mice receiving adoptively transferred splenocytes from germ-free mice compared with splenocytes from specific pathogen-free (SPF) mice, showing the importance of the microbiome in influencing this phenomenon. Finally, a study of rare brain parenchymal CD4+ T cells found that SPF mice housed with “dirty” mice had higher numbers of brain parenchymal T cells than SPF mice, suggesting that the gut microbiome either directly or indirectly influences CNS T cell number (Pascuito et al., 2020). Thus, a number of studies provide direct and indirect evidence of homeostatic, and perturbation-inducible recruitment of intestinal lymphocytes to the CNS and meninges. Such recruitment in vivo may protect the host from the development of infective meningitis in the context of bacteremia.

In addition to supplying the meninges with gut-educated immune cells, there are several other mechanisms by which the intestine may influence meningeal immune cells; blood-borne metabolites and pathogen-associated molecular patterns arising from the intestinal microbiome may reach dural cells via its fenestrated vasculature. In keeping with this concept, transplantation of Parkinson’s disease patient microbiome into α-synuclein transgenic mice led to accelerated disease progression, proposed to be due to the effects of microbial-derived short-chain fatty acids (Sampson et al., 2016). In addition, the vagus nerve directly supplies the gut, traveling through the meninges on its journey. An increasing number of studies suggest that this conduit may support the retrograde transmission of immunological information back into the CNS (Breit et al., 2018; Houser and Tansey, 2017), with the potential to communicate with meningeal immune cells en route (Fig. 2).

Conclusion
With its substantive populations of IgA-producing plasma cells, as well as ILC2, γδT17, and antigen-experienced T cells, including T regs, the immune composition of the peri-sinusoidal dura evokes notable comparisons with the intestinal lamina propria. The gut is an organ containing trillions of microorganisms, including bacteria, fungi, and viruses, many of which have beneficial effects, and must therefore be tolerated by the intestinal immune system, which is rich in regulatory cells. However, this intimate relationship and close proximity to the microbiome inevitably comes with risks, with intestinal organisms the most common cause of bacteremia. The vasculature of the meninges and CNS contain several areas with fenestrated endothelium, including regions of the dural venous sinuses that also have a low flow rate of blood. These factors confer vulnerability to invasion by circulating microbes. We propose that this has evolutionarily led to the establishment of close links between the gut and meninges, to prime the CNS defense against the most likely invaders. This paradigm is exemplified by the dural venous sinus IgA defense system, where the antibody repertoire mirrors that of the gut. It is notable that the bacterial species that overcome this defense system to cause meningitis both originate from a non-gut source and have evolved to express IgA-cleaving proteases (Kilian et al., 1979; Mulks et al., 1982; Mulks et al., 1980). The immunoregulatory profile of gut immune cells may also have benefits for the CNS in limiting inflammation and the
collateral damage associated with it. Although there have been a number of exciting breakthroughs in the area in recent years, a number of questions remain to be resolved: What are the cues guiding intestinal immune cells to the dura? Where do they enter? To what extent do gut-derived immune cells move from the dura to the brain and spinal cord in response to different CNS-intrinsic perturbations, and is this process helpful or harmful? How do microbial metabolites influence different meningeal immune cell subsets? Answers to these questions will no doubt emerge in this dynamic area of immunology, and may well reveal how this axis could be harnessed or attenuated therapeutically in neurological and psychiatric diseases.

Acknowledgments
M.R. Clatworthy is supported by a Medical Research Council Research Project Grant (MR/S035842/1), a Wellcome Investigator Grant (220268/Z/20/Z), and by the National Institute of Health Research (NIHR) Cambridge Biomedical Research Centre. R. Di Marco Barros and M.R. Clatworthy are supported by an
NIHR Research Professorship (RP-2017-08-ST2-002). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care.

Author contributions: M.R. Clatworthy conceived the structure/content. R. Di Marco Barros and M.R. Clatworthy wrote the manuscript. Z. Fitzpatrick contributed to the section on meningeal B/plasma cells. M.R. Clatworthy designed and generated a first draft of the figures. R. Di Marco Barros produced the Biorender figures.

Disclosures: The authors declare no competing financial interests.

Submitted: 25 November 2021
Revised: 26 January 2022
Accepted: 26 January 2022

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