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Research paper

The importance of knowing you are sick: Nanoscale biophotonics for the 'other' brain

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ABSTRACT

A great new frontier in biomedical science has recently been discovered that requires the attention of technologists from diverse backgrounds to equip scientists with the tools needed to explore this great uncharted area. This new expanding domain is the exploration of the neuroimmune cells of the central nervous system, and their real-time function and contributions to the health and disease of the brain and spinal cord. Glia, once thought of as mere structural supports for the brain, are now appreciated to actively contribute to brain function. However, the true complexity of this system is still hidden from close examination, owing to a range of technological and methodological limitations. Here, some of these opportunities and challenges are outlined to expose the micro and nanoengineering community to this dynamic area of research, and to encourage innovation and technology application in the research of the "other brain".

1. The next frontier in understanding the brain – the neuroimmune interface

At the turn of the millennia a sea-change occurred in neuroscience research, owing to the acknowledgement of key bidirectional signaling that occurs between neurons and a host of immunocompetent cells present in the central nervous system, including glia (microglia, astrocytes and oligodendrocytes), endothelial cells, perivascular macrophages and infiltrating T cells [1–3]. Neuroimmune cells of several types engage intimately with neuronal processes to maintain brain homeostasis. These cells form the structures that create and maintain the blood brain barrier, neuronal myelination and encapsulate synapses [4]. These cells also perform regular brain surveillance for cellular disturbances, damage or infection [4], and can contribute to drug responses [5,6], stress and depression [7] and exaggerated pain states [8].

2. No more brain glue

Once thought of as just "brain glue", glia, were overlooked for playing a meaningful role in the normal function of the central nervous system [4]. Moreover, the brain and spinal cord were concluded to be an immune privileged organ with classical peripheral immune cells precluded from crossing the blood brain barrier and circulating through the central nervous system [2]. However, it is now appreciated that both immune-like glial cells and peripheral immune cells are far more than passive bystanders in the brain or mere components of the extracellular matrix, and have been shown to modulate neurotransmission and hence complex behavioural responses orchestrated by the central nervous system [1,9,10].

The intimate spatial, trophic and signaling relationship that is formed between the neuronal and immune systems of the central nervous system is best described as the neuroimmune interface [2]. This multicellular functional unit, in its simplest form, is replicated billions of times throughout the central nervous system and can be thought of as comprising neuronal processes (including both pre and post synaptic bodies), astrocytic projections and microglial surveillance, possibly with selective migration of peripheral immune cells to unique cellular events to protect the brain, and contribute to behavioural modulation [11].

3. Astrocytes

Within the neuroimmune interface the majority of research has focused on the role of astrocytes and microglia, and to a lesser extent on that of T cells and endothelial cells [4]. Astrocytes are the most abundant cell type in the central nervous system (CNS). In addition to providing structural support, promoting formation of the blood brain barrier and regulating cerebral blood flow, astrocytes contribute to synaptic transmission, provide trophic support and promote repair of neuronal systems [12]. They also maintain homeostasis in the extracellular environment by regulating the concentration of neurotransmitters and ions in the synaptic cleft [13]. Their morphology and functions are highly polarized and heterogeneous [14]. As will be discussed, each of these features of astrocyte biology make them exquisitely challenging

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to explore *in vivo*, and very complex to replicate *in vitro* with current technologies [15].

4. Microglia

Microglia are the tissue specific phagocytes of the CNS [2,16]. They exhibit constitutive and regional heterogeneity throughout the parenchyma, presumably to coordinate diverse responses to insult, or in dynamic response to the microenvironment of their local neuroimmune interface [17,16]. Under a basal surveillance state, the cytoarchitecture of microglia allows them to continuously sample the extracellular space for perturbations [16]. Their transition to a state of reactive gliosis involves changes in cell number, morphology, phenotype and motility, the expression of membrane-bound and intracellular signaling proteins (for example, mitogen-activated protein kinases), and the release of immunoregulatory products, such as cytokines and chemokines [18]. Each of these cellular processes can occur with significant speed and potency, making quantification of these events within specific neuroanatomical compartments challenging. As such, we are presented with a similar case for astrocytes, with microglia remaining challenging to investigate owing to their reactivity to exogenous stimuli, and willingness to change their function rapidly [15,19].

5. Novel origins of brain health and disease

This unique spacial position of these immune-like cells makes them pivotal to the health and disease of the brain [13]. Complementing this neuroscience revolution, and the movement away from viewing the brain as an immune privileged organ, has been the acknowledgement of a key bidirectional communication between the brain and the peripheral immune system [2,20]. These discoveries have developed from an appreciation that how we think, can modify peripheral immune function [21], and how our immune system functions can change the way we think [22]. In each of these cases there is a key role for the neuroimmune interface in translating peripheral to central neuronal and immune messages.

6. How do we know we are sick?

The apparently simple question of "how do we know we are sick?" now has its origins and answers within the underappreciated realm of the neuroimmune interface [23]. It is the neuromodulatory capacity of these cells that allow the change of behavior during times of illness [24]. These behavioural adaptations have been linked to changes in cognitive function, mood, depression, anxiety, pain, addiction and reward [7,25]. However, we have a paucity of tools to examine the function of these cells individually, or within networks within living, behaving models of health and disease [15].

7. Nanoscale Biophotonics for the "other" brain

The current tools available to the neuroscience and immunology research fields are insufficient to explore the real-time function of these underappreciated cells of the "other" brain in preclinical and clinical models [26]. The signaling events that occur at the neuroimmune interface engage high potency large peptides, and short lived reactive species which are not detectable with the quantitative or spacial resolutions needed to understand how this system functions. Such technological advances and breakthroughs cannot be achieved by researchers acting in isolation. Instead, it is through transdisciplinary communities such as those created by the Micro and Nanoengineering community and through large scale funding schemes like the Australian Government's Centres of Excellence scheme that such challenges can be met. This is the space in which the Australian Research Council Centre of Excellence for Nanoscale BioPhotonics has a key mission to deliver biophotonic tools to open new windows into the neuroimmune interface.

8. Why Biophotonics for the "other brain"?

The transdisciplinary discoveries and applications derived from the Micro and Nanoengineering and Biophotonics communities can harnessed light-based imaging and sensing tools to capture information from biological processes over scales ranging from events occurring at the single molecule (nano), through to secondary and tertiary biological structures (micro) to subcellular and cellular anatomy (macro). This is the range of scales that need to be explored in order to capture the complexity of the neuroimmune interface. There are however inherent opportunities and pitfalls in the push and pull of this technology development which must be considered.

9. Pushing the boundaries of sensitivity and specificity

Health and disease in biological organisms can be symptomatically observed on a macro and systems biology level. That is we can actually see many illness present in ways visible to the naked eye. However, in every case the origins of these disease states are initiated and maintained by molecular events often at scales below the diffraction limit of light. These originating events are of great relevance to the neuroimmune synapse owing to the profound amplification of immune signals.

These events can take many forms. For example, the genetic class selection and maturation that drives antibody antigen refinement occurs within the nucleus of a circulating cell *via* changes in DNA sequence. Other changes can occur to lipid that is oxidised within the myelin membranes of the neuronal tracts of the spinal cord. Such an event can lead to activation of microglial reactivity that contribute to the early events which snowball into neurodegenerative disorders like Multiple Sclerosis and Motor Neuron Disease.

Advances in imaging technologies, and data processing are allowing some of these events to be visualized. But just as these single molecular events are the origins of the disease, they occur within a complex systems biological clouds of many parallel events. Importantly, in many cases there are a multitude of contributing or perhaps counter-regulatory molecular events that sum to create the full representation of the disease presentation. Unfortunately for those of us who wish to see these events in the central nervous system, they occur in the highly light scattering surrounds of brain and spinal cord tissue, encased within the opaque and mechanically important bone structures of the scull and spinal cord. Therefore, capturing this discrete nano-micro molecular information in the future in the larger biological context presents a major technical and computational challenge, especially if this work is to be conducted in real-time in a behaving animal model.

10. Repeated sampling, multiplexing and multimodal systems

As these complex neuroimmune synapse events are explored, there is continual pressure to gain greater parallel streams of information from the biological processes at the nanoscale. This need is not unique to the study of the "other brain" and as such there have been profound advancements in multimodal data collection made available to the medical science field, with technology comprising several imaging and sensing modalities in one platform. These multimodal imaging and sensing approaches are beginning to allow for complex *a priori* hypothesized events to be quantified. Hypothesis free, sample phenotyping approaches are also available through the use of approaches such as Raman and tissue auto-fluorescence acquisition [27]. These multiplexing technologies are in high demand when examining the neuroimmune interface as we face compounding issues of a scarcity of tissue, owing to the regional selectivity of cellular functions. This has driven the creation of a great range of synthetic biology and chemically derived spectrally distinct fluorescent and luminescent probes that allow for parallel sensing and imaging [15]. However, the ability to separate these probes spectrally is limited. As such, new tools that