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MEETING REPORT

INFLAMMATION RESEARCH: NEW HORIZONS AND TRANSLATIONAL CHALLENGES

HIGHLIGHTS FROM THE SOCIETY OF MEDICINES RESEARCH SYMPOSIUM, HELD ON JUNE 5TH, 2014 – GLAXOSMITHKLINE, STEVENAGE, UK

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SUMMARY

Inflammation is part of a complex biological response of tissues to stimuli such as pathogens, irritants and damaged cells. It is one of the most fundamental and well-studied pathological mechanisms. Still, after decades of research in both academia and industry there remains a high unmet need for effective antiinflammatory therapies. In addition, recent studies have highlighted that in a variety of chronic conditions, inflammation is not just a mere bystander, but an integral part of pathology that is likely to contribute to disease progression and fatality. One of the major challenges in drug discovery is to harness available data and generate approaches that have the promise to translate from bench to bedside. This meeting brought together a number of key opinion leaders from both industry and academia to outline the current thinking about inflammatory processes and how they may be tackled to bring benefit to patients.

Key words: Inflammation – Multiple sclerosis – Traumatic brain injury – Alzheimer's disease – Inflammatory bowel disease – Rheumatoid arthritis – Pharmacological modeling

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MINING THE IMMUNE RESPONSE IN REMYELINATION AS A SOURCE OF POTENTIAL TARGETS FOR DRUG DISCOVERY IN MS

Professor ffrench-Constant described the challenges of developing an effective treatment for multiple sclerosis (MS) against the background of an inflammatory response to the damage caused by the disease. Immune modulation treatment helps to reduce MS relapses but does not change the progression to neurological disability, which is correlated to axonal degeneration. Remyelination is carried out by oligodendrocyte precursor cells (OPCs), which are required to proliferate, migrate into the demyelinated lesion, differentiate into mature oligodendrocytes and attach to axons to form the compact myelin sheath. The process of remyelination can fail at any of these steps. Professor ffrench-Constant described MS pathologically (inflammation, mitochondrial damage, demyelination and axonal loss) and progressive MS in more detail. Progressive MS has two phases of the disease: a relapsing-remitting phase and a chronic progressive phase. Currently, there are no effective treatments for progressive MS and the remainder of the talk focused on the series of models that Professor ffrench-Constant's group utilizes to activate the regenerative innate immune system, but not the adaptive immune system, in order to assist the identification of novel therapies to treat MS.

At the early stages of progressive MS, the body has the capacity to induce myelin to repair. In animal studies, shadow myelin plaques have been described which have the capacity to remyelinate. It has been demonstrated that OPCs become activated, proliferate and enter the plaques in large numbers. Remyelination does indeed occur, but the new myelin is thinner, and promotion of repair requires integration of cells into the area of damage. In older animals, remyelination is slower and incomplete. Repair of a demyelination injury in older animals has been accomplished by parabiosis, which involves joining together the circulation of old and young animals. As part of the remyelination process, a switch occurs in the innate immune response, resulting in domination by M2 antiinflammatory or immunoregulatory macrophages and microglia. Depletion of these M2 microglia and macrophages in animals results in an impairment of remyelination. Depletion of M2 macrophages also results in a decrease in the activin signaling pathway.

Professor ffrench-Constant's group utilized an in vivo model of the innate immune response in which zymosan-induced macrophage activation in the retina promotes myelin sheath formation by oligodendrocytes generated from transplanted precursor cells (1). Using this model, several cytokines –CXCL13, ET-2, CCL20 and CXCL2– were observed to be significantly upregulated in zymosan-treated retinae by microarray analysis. When tested in a cerebellar slice culture model, CXCL13 and ET-2 promoted myelination, and the endothelin B receptor (ET-B) agonist BQ-3020 also promoted remyelination.

A number of assays are currently under further development within the group in Edinburgh, including a myelin sheath formation assay, co-culture of OPCs and neurons, and the use of zebrafish to investigate pruning of myelin.

In conclusion, it will be important to stratify MS patients into cohorts that distinguish these patients by their innate ability to regenerate myelin. Different cohorts may benefit from different therapeutic strategies involving combinations of antiinflammatory, neuroprotective and remyelination therapies tailored to their specific disease indications.

NETWORK DYSFUNCTION AND INFLAMMATION AFTER TRAUMATIC BRAIN INJURY

Professor Sharp's presentation showed how using magnetic resonance imaging (MRI) and positron emission tomography (PET) were able to reveal subtle pathologies within the brain indicative of traumatic brain injury (TBI). These points were largely illustrated using a case study of a female patient who was suffering from cognitive disorders that were preventing her return to the workforce after suffering brain injury from an accident. Using state-of-the-art diffusion tensor imaging, abnormalities indicative of chronic inflammation were identified, particularly in subcortical regions of the brain. Further studies using PET were able to identify microglial activation as playing a key role in TBI-induced chronic inflammation (2). These points served to illustrate the chronic nature of TBI and the clinical need for modifying persistent inflammatory responses that can be attributed to debilitating cognitive deficits in patients suffering from this injury.

Professor Sharp then further developed these ideas by explaining how TBI causes neurological impairment by disrupting intrinsic connectivity networks (ICNs) (3), regions of the brain that show temporally correlated neural activity. Like Alzheimer's disease (AD), TBI-associated neurodegeneration results in the formation of lesions, including amyloid plaques. Imaging data showed that TBI and AD share some common regions of the brain affected by neurodegeneration, but also differences that could be used in diagnostic assessments. An improved characterization of the disruption of the integrity of the network in individuals affected by TBI should have great potential to improve prognostication, and also guide current treatment regimens and the development of new therapeutics. This work also highlights the heterogeneity of TBI and why effective treatment of this disease requires a personalized evaluation for each patient (3).

THE IMPACT OF SYSTEMIC INFLAMMATION ON THE HEALTHY AND DISEASED BRAIN

Professor Perry introduced the physiology and phenotype of the brain's resident macrophage population, known as microglia. These cells are tightly controlled by the local environment and maintained in a quiescent state pending activation by a range of cytokines and a diverse range of cellular expressed proteins, such as triggering receptor expressed on myeloid cells 2 (TREM-2). Activation of these cells by the innate immune response leads to proliferation and adoption of very diverse and highly plastic phenotypes. Proliferation is mediated by colony-stimulating factor 1 (CSF-1), via the CSF-1 receptor, and interleukin-34 (IL-34). The concept of microglial "priming" was discussed, leading to a proinflammatory phenotype which is then sensitive to secondary inflammatory stimuli, producing exacerbated inflammatory responses. This concept was demonstrated in an animal model of prion disease, where CSF-1 produced activation and proliferation of microglia, which was then blocked by an antibody to the CSF-1 receptor. Subsequent induction of systemic inflammation resulted in exaggerated cytokine production and an enhanced "sickness behavioral syndrome". Treatment with the CSF-1 receptor kinase inhibitor GW-2580 reduced proinflammatory markers, reduced cell death and sickness behaviors, and ultimately increased lifespan in these prion-infected animals. This type of phenomena has also been seen in AD brains. Furthermore, genome-wide association studies have highlighted a key role for the innate immune system in AD. It is postulated that aging and/or neurodegenerative processes have a priming effect on the human brain. Systemic inflammatory events then lead to an exaggerated response and maladaptive neuroinflammation, which leads to progressive neuronal damage. Thus, an enhanced understanding of these systemic/brain innate immune responses is needed to permit the development of therapeutic interventions to attenuate this priming phenomena, and subsequent neuroinflammation and progressive neurodegeneration seen in diseases such as AD.

SYSTEMIC INFLAMMATION IN ALZHEIMER'S DISEASE: CLINICAL ASPECTS

Continuing the theme of inflammation in AD, Professor Holmes discussed the clinical evidence to substantiate the hypothesis set forward by Professor Perry. Clinically, there is clear evidence of communication between the systemic inflammatory system and the brain, leading to sickness behaviors. Imaging studies have demonstrated that low-grade inflammation brought about by lipopolysaccharide

(LPS) leads to activation of brain structures involved in environmental monitoring and enhanced translocator protein (TSPO) PET ligand binding (a marker of neuroinflammation). Generally, low-grade inflammatory events have little effect on the normal brain, but in the aged brain or in conditions such as neurodegenerative disease, loading of aberrant proteins leads to neuroinflammmation and priming of the innate immune system. In a clinical study of 300 AD patients, infections were monitored together with blood markers of inflammation over a six-month period. Longitudinal cognitive performance of these individuals was also assessed, and it was seen that infection was directly correlated with decreased cognitive performance and enhanced tumor necrosis factor (TNF) levels. Neuropsychiatric performance also worsened, especially depressive and anxiety symptoms. Since aged populations are likely to present with many proinflammatory comorbidities, such as diabetes, atherosclerosis, obesity and vascular disease, it may be important to limit the systemic inflammatory events to reduce the exaggerated "primed" inflammatory responses in the brain. Since the role of TNF in these responses seems to be established, Professor Holmes group undertook a small study examining the impact of the TNF binding protein etanercept (Enbrel®) in Alzheimer's patients over a six-month period. Data from this study will be reported at the forthcoming Alzheimer's Association International Conference. Initial indications appear favorable. Therefore, novel therapeutic strategies aimed at attenuating ongoing priming of the brain's microglial populations and low-grade systemic inflammation may be effective in slowing the progression of neurodegenerative conditions such as AD.

TARGETS IN INFLAMMATORY BOWEL DISEASE

Dr. Keshav discussed the challenges in understanding the disease pathogenesis of inflammatory bowel disease (IBD) and translating new findings into better treatments. His talk began with an overview of the current clinical landscape. Specifically, corticosteroids, 5-aminosalicylates and anti-TNF biologics have converted the two major forms of IBD, ulcerative colitis (UC) and Crohn's disease (CD), from life-threatening diseases to chronic illnesses with well-defined treatment options and predictable outcomes. However, UC and CD still cause a significant cost to the healthcare system, and there remains a high unmet need for better tolerated treatments that ensure prevention of relapse. For example, in UC, the rate of colectomies has not changed despite significant reductions in mortality, indicating that while the disease is less deadly, comorbidities have not appropriately been addressed.

Dr. Keshav then pointed out that the current model of IBD may be over simplistic, concealing complexity and heterogeneity that hampers clinical research. In particular, more than 160 IBD susceptibility genes are known to date, some of which only predispose individuals to specific IBD subtypes (e.g., NOD2 and ileal CD). This observation suggests that IBD may be a consequence of many different diseases that require different treatments. A personalized medicine approach is therefore needed. Finding such treatments based on genetics is, however, challenging, as it is unclear, for example, whether mutations cause a gain or a loss of function. Still, research has progressed now to a level where there is a much better understanding of pathological mechanisms, such as the interaction between the immune system and gut bacteria, the role of Paneth cells in the small intestine, and the role of Th17 cells in IBD.

In the final part of his talk, Dr. Keshav introduced the concept of targeting immune cell infiltration into the gut wall as a new way to specifically treat intestinal inflammation. Such an approach has the benefit of inhibiting the immune response in the gut without risking the development of systemic immune suppression. One therapeutic agent that uses this approach is vercirnon (CCX-282) (ChemoCentryx), a specific, orally administered C-C chemokine receptor type 9 (CCR-9) antagonist that regulates migration and activation of inflammatory cells in the intestine. In a multicenter phase II clinical trial that enrolled patients with moderate to severe CD (PROTECT-1) (4), vercirnon significantly reduced disease severity in an induction trial. Also, more patients receiving vercirnon were in clinical remission by the end of 36 weeks compared to placebo. The agent was well tolerated, without increased rates of infection, suggesting that a gut-targeted approach could reduce side effects. However, later testing by GlaxoSmithKline (GSK) in a phase III induction trial (SHIELD) was unsuccessful and the effect of vercirnon on maintenance of remission was not tested. There were a number of differences in trial design that may explain this failure, and vercirnon is still being investigated by ChemoCentryx in the clinic. Besides vercirnon, there are a number of biologics in IBD trials that also target immune cell trafficking to the gut: vedolizumab (Millennium Pharmaceuticals/Takeda), a monoclonal antibody that binds to integrin alpha-4/beta-7, and etrolizumab (Roche/Genentech), another monoclonal antibody that selectively binds the beta-7 subunit of the heterodimeric integrins alpha-4/beta-7 and integrins alpha-E/beta-7. Both of these antibodies have shown efficacy in IBD trials. For example, in a recently published phase II trial etrolizumab was shown to give efficacy at week 10 compared to placebo (5), and phase III studies have been planned. Targeting integrins may therefore be at the forefront of a number of new approaches to tackle this heterogeneous disease by going after gut-specific targets.

EPIGENETICS IN RHEUMATOID ARTHRITIS AND BEYOND

Dr. Prinja started his talk with a description of the Immuno-Inflammation Therapy Area based at GSK. He laid out a vision to discover and develop transformational medicines to meet unmet needs for both mainstream and rare diseases through cure or remission.

Epigenetics is broadly defined as a study of heritable changes in gene activity not involving any alterations of the primary DNA sequence. Epigenetics is divided into distinct functional groups: epigenetic writers which modify DNA and histones (histone acetyltransferases, HATS); epigenetic readers with specific protein domains that recognize DNA or histones (bromodomain-containing proteins recognize the lysine tail when it is deacetylated); and epigenetic erasers that can delete existing modifications to make way for new modifications (histone deacetylases). There are epigenetic differences picked up between healthy and disease tissues.

Rheumatoid arthritis (RA) pathogenesis has been shown to involve many cell types, including macrophages, fibroblast like synoviocytes (FLS) and T cells. It has been shown that the RA synovial fibroblasts appear to orchestrate inflammation and drive destruction of cells within the pannus of an arthritic joint. Epigenetic changes within the RA FLS cells have been shown to be involved in RA pathology, and interfering with epigenetic pathways could represent a novel therapeutic intervention for RA.

Dr. Prinja then described an example of an epigenetic mechanism involving the bromodomain family of proteins (including BRD2, BRD3 and BRD4), which are critical to the assembly of histone acetylation-dependent chromatin complexes that regulate inflammatory gene expression. A potent inhibitor, I-BET762, was described which protected mice from LPS or Salmonella triggered cytokine expression and mortality (6). Currently I-BET762 is in early clinical trials for the treatment of NUT midline carcinoma (NMC) a rare, aggressive and lethal tumor with a median overall survival of 6.7 months. Selectivity is key, and work is continuing to profile selective bromodomain inhibitors to explore their utility as therapeutics for treating a variety of inflammatory diseases.

APPLICATIONS OF QUANTITATIVE SYSTEMS PHARMACOLOGY MODELING TO SUPPORT INFLAMMATORY DISEASE RESEARCH

Dr. Kudrycki presented a systems biology approach developed by Rosa & Co. that can aid drug research and development. The approach consists of the construction of a physiological mechanistic model that utilizes relevant information about cell, organ and organism processes in health and disease. Drug property information (e.g., PK/PD) can be included in the model to build "virtual patients", and simulate in vitro and in vivo experiments including clinical trials. One particular approach, PhysioPD, incorporates perspectives from systems engineering, pharmacology and drug development. PhysioPD models provide the opportunity to explore permutations of future study designs and alternative hypotheses about mechanisms of action. These models support the prediction of efficacy, identification of biomarkers, optimization of clinical protocols and identification of responsive subpopulations.

To explain the application of this approach and its utility in inflammatory diseases, Dr. Kudrycki presented a case study in which a PhysioPD model was built to assess the potential impact of targeting neovascularization and inflammation in RA. While anti-TNF agents have been successful in the treatment of RA in some patients, there is a need for new therapeutics with improved efficacy against broader patient populations. In addition to the various mediators of immune and inflammatory pathways, angiogenesis may contribute substantially to the pathogenesis of RA. The combination of an anti-angiogenic agent with an anti-TNF function into one molecule could be more efficacious without the risk of severe immunosuppression. To assess this possibility, Rosa built a virtual model of inflammatory pathways and angiogenic signaling that included, among other parameters, infiltration of macrophages into the synovium, accumulation of hypoxia-inducible factors (HIFs) and activation of pro-angiogenic genes like vascular endothelial growth factor (VEGF). Increased leakiness of newly formed blood vessels was also taken into account. The system was then used to explore the potential difference in responses between an agent targeting TNF alone vs. a bispecific antibody that also targets angiopoietin-2 (Ang-2), an important angiogenic factor. Primate PK data for these antibodies were included to model dosing. Finally, a number of "virtual patients" were created that reflected potential differences in response, e.g., the interaction between TNF levels and Ang-2 production or the alteration of vessel leakiness in response to treatment. Based on these models, Rosa was able to provide guidance about a potential treatment regimen, and the targeting of specific patient populations. In summary, quantitative systems pharmacology provides new insights into complex mechanisms of action that can influence the direction of research programs and study strategies.

DISCLOSURES

J. Holder, P. Weber, L.A. Dawson and K.A. Brown are paid employees of their respective companies or universities. All authors are SMR Committee members for which no remuneration is paid.

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