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2010 Keystone Symposium Meeting Report: Alzheimer's disease beyond A β :

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Abstract

Many of the Alzheimer's disease (AD) clinical trials have made it far enough down the pipeline to allow conclusions about targeting the amyloid- β peptide (A β) as a therapeutic approach. Based on these results, it is becoming clear that a multifocal approach to AD treatment is probably necessary. However, critical discussion beyond A β is necessary to enable the next wave of AD therapeutic targets. For this reason, the 2010 Keystone Symposium, 'Alzheimer's Disease Beyond A β ', was organized by JoAnne McLaurin and Tony Wyss-Coray to spark topical discussion and debate. While researchers struggled to get beyond that ever-present pathognomonic feature of AD, new and exciting evidence was presented that raised our awareness of what is around the corner for next-generation AD therapeutics beyond A β . This report will describe some of the highlights from Copper Mountain Resort throughout the meeting period of 10–15 January 2010 in Colorado (USA). Despite illuminating scientific presentations and intense discussions, a number of important questions remain concerning the best biomarkers and targets to focus on, and when and how to therapeutically intervene.

Keynote addresses: defining 'beyond A β '

Amyloid plaques are a defining feature of Alzheimer's disease (AD), so it was clear from the outset that it would be about as difficult to get beyond the amyloid- β peptide (A β) in AD as avoiding rarefied air and high altitude during the meeting proceedings. In the first keynote, Dora Games (Elan Pharmaceuticals, CA, USA) presented an overview of 'beyond A β ', and stressed the importance of pathways that are entirely independent of A β yet critically important in AD pathobiology, including apolipoprotein E (APOE), caspases and glycogen synthase kinases. She also described additional pathways that act synergistically with and complement A β , such as brain inflammation and tauopathy. Games provided an update on active and passive A β 'immunotherapy' approaches that were initiated over a decade ago by Dale Schenk and

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other members of the Elan/Wyeth team. While this approach has faced significant setbacks, including adverse events such as aseptic meningoencephalitis and cerebral microhemorrhage, A β vaccination in its various forms does generally appear to clear cerebral amyloid (at least partly via a brain-to-blood route involving capillaries and small arterioles) and may reduce cognitive impairment. We anxiously await results from a number of A β immunotherapy clinical trials, including the passive A β vaccine bapineuzumab. Finally, she discussed recent findings from Donna Wilcock and Carol Colton in nitric oxide synthase 2-deficient AD model mice, where deficiency in this gene produces tauopathy, neuronal loss and behavioral impairment, and these pathological features all seem to be responsive to A β vaccination in this model.

In the second keynote address, Lennart Mucke (University of California, San Francisco, CA, USA) opened with an overview of AD as a proteopathy, characterized by misfolded A β and tau proteins. He stressed that strategies just aimed at blocking A β may not have a broad enough clinical impact on AD, and that other approaches must be considered. Mucke submitted that he was not exactly sure what 'beyond A β ' meant, but he offered two interpretations: downstream of A β or besides A β . Examples of the former included tau, phospholipase A2 and abnormal neural networks; while the latter could include APOE4 and other amyloid precursor protein (APP) metabolites. There was a strong focus on which APP metabolites cause disease and he presented null data on mice deficient in the APP metabolite C31, which brought his group to A β as the key disease-perpetrating APP product. However, the question that has been raised is: precisely how does A β cause disease? The answer may come from studies that Mucke conducted in collaboration with Jeffrey Noebels, where they found striking epileptiform activity and seizures in A β -overproducing mutant human APP transgenic mice, which can be interpreted as a symptom of abnormal neural networks brought on by A β . He also presented results from newborn granule neurons in mutant human APP-overexpressing mice, where these cells develop abnormally and early inhibition of GABAergic signaling prevents this, while late-stage inhibition of calcineurin restores maturation. Finally, he focused on a strategy to reduce tau protein levels, which does not impact plaque burden in transgenic mouse models of AD, yet improves memory by opposing neuronal overexcitation.

Should we focus on treatment or prevention?

As we move forward into this modern era of AD therapeutics, a key issue that must be grappled with is whether to invest in strategies for prevention or treatment of active disease. Todd Golde (University of Florida, FL, USA) critically considered this issue in his presentation. First, he gave his view on the A β hypothesis and its corollary, the A β aggregate hypothesis. Both of these hypotheses purport that A β in one form or another is the driving pathoetiological force in AD, and that A β -lowering strategies will, in principle, produce downstream therapeutic benefit(s). However, Golde cautioned that just because an A β -based therapy fails does not necessarily mean that the A β hypothesis itself is invalid. Yet, he stressed the need for additional therapeutics aimed at other pathways, including tau, and he raised significant problems with the A β hypothesis. Some of these issues stem from the inadequacy of the mouse models; that, despite having severe A β burden, the mice do not get much tau pathology or neuronal loss. Also, cognitive disturbance in mouse models of AD is not terribly robust, especially given their high cerebral A β loads. These issues recall what Karen Duff has maintained for years: that 'mouse-zheimers' is not so much a model of AD, but rather a model of cerebral amyloidosis.

He then launched into a discussion of what he terms the 'treatment versus prevention paradox'. He presented thought-provoking results where his group treated three different age cohorts of AD model mice with a γ -secretase inhibitor and then assessed cerebral amyloid. γ -secretase inhibition was able to reduce A β deposits by up to 50%, but only when administered prophylactically to the youngest cohort of AD model mice. Thus, it seems that A β -directed

therapies will work best when initiated relatively early in the course of the disease. The idea is that early treatment is able to reverse plaque nucleation events, whereas later intervention fails in this regard. Further validation of this concept came from Joanna Jankowsky and David Borchelt's inducible mutant human APP transgenic mice, in which the transgene can be switched 'on' or 'off' using tetracycline analogs (e.g., doxycycline), and from a collaboration with Pritam Das, where recombinant IL-6 was expressed early in brains of traditional-variety mutant human APP transgenic mice and was beneficial in this scenario.

Yet, a presentation by Roxana Carare (University of Southampton, Southampton, UK) suggested that A β can be effectively cleared through the cerebral vasculature, raising the possibility that active AD treatments targeting this pathway could be efficacious, in principle. She opened with a discussion of vascular A β and cerebral amyloid angiopathy pathogenesis, and mentioned that A β is typically found in the tunica media and glial limitans in leptomeningeal arteries within AD patients' brains, suggestive of attempted brain A β clearance via a blood route. Furthermore, she detailed results from A β immunotherapy approaches, which seem to reduce parenchymal A β , but increase cerebral amyloid angiopathy pathology; again, indicative of brain-to-circulation A β clearance. Why does this clearance pathway ultimately fail to remove cerebral amyloid in AD patients? To begin addressing this question, Carare designed two sets of experiments. In the first experiment, her group peripherally administered a dextran tracer to AD transgenics and found that the tracer was absorbed by cerebral plaques and was detected in vascular basement membranes that are generally devoid of A β deposits. These results raise the question of whether there is bidirectional communication between the brain and the blood; that is, perhaps A β traffics both ways. In the second approach, she utilized ovalbumin immunization in AD transgenic mice and found – surprisingly – that ovalbumin immune complexes in cerebral vessels did not interfere with A β drainage from brain to blood. She concluded by stating that therapies that facilitate A β drainage through cerebral capillaries and arteries may be effective for AD.

Biomarkers, biomarkers, biomarkers...

Irrespective of whether drugs are used for AD prevention or active therapy, development of biomarkers is critically important to reliably identify individuals that will go on to develop the disease and to track the course of therapeutic intervention. William Jagust (University of California, Berkeley, CA, USA) presented data on the use of molecular imaging as a valid and valuable biomarker. Specifically, he focused on use of [C11] Pittsburgh compound B ([C11] PiB) to distinguish healthy elderly from individuals with mild cognitive impairment (MCI) or AD. He presented compelling evidence showing that [C11]PiB brain scan intensity increases with age and correlates with cerebrospinal fluid A β abundance. Interestingly, cutoff analyses showed that approximately 20% of normal individuals have a positive PiB scan, suggesting that these may be the individuals that are 'on the cusp' of developing MCI or AD. While there was no clear correlation between brain region-specific PiB signal and reduced glucose metabolism, nor between PiB scans and severity of dementia, he reported that fluorodeoxyglucose scans did correlate well with degree of dementia. Furthermore, early-onset (familial) AD cases had more evidence of glucose hypometabolism than late-onset (sporadic) cases, but there was no real difference in amount of PiB⁺ amyloid between these cohorts. Finally, he shared data demonstrating that, in healthy elderly individuals, increased PiB signal correlates with small hippocampal volume and increased severity of episodic memory disturbance. These data led to the conclusion that A β pathology is an early event associated with cognitive decline, but that cognition is more closely related to measures of network degeneration rather than to A β itself.

Later on during the meeting, Daniel Skovronsky (Avid Radiopharmaceuticals, PA, USA) focused on newly developed A β molecular imaging compounds that may be superior to PiB.

One compound, AV-45, was selected for further analysis based on favorable brain entry and washout results. This compound was exquisitely sensitive to amyloid and worked in both humans and in a transgenic mouse model of AD. Furthermore, the compound had high test–retest reliability and not only cleanly separated AD patients from controls, but was also able to robustly detect MCI. Clinical studies using AV-45 revealed that, in both AD patients and in healthy controls, amyloid is one of the best correlates with memory impairment and cognition. In addition, he presented intriguing results that *APOE4*, aside from its well-documented association with risk for developing AD, is also a risk factor for amyloid, while *APOE2* significantly protects against cerebral amyloid accumulation.

While molecular imaging techniques provide a rich dataset that gives insight into cognitive status, these techniques are costly and require specialized imaging equipment and neuropsychological expertise – both of which can be in short supply at smaller clinics and universities. But what if a simple plasma biomarker panel was available as an AD diagnostic? According to Tony Wyss-Coray (Stanford University, CA, USA), this could soon be possible. His group has identified a ‘plasma communicome’ of aging and of dementia. He opened by stressing the twofold importance of signaling protein communicomes in the context of AD: their use as disease biomarkers and as tools to inform disease biology. Wyss-Coray also clarified that his panel of plasma proteins is not just a set of proteins involved in inflammation, but is rather a network of signaling proteins that participate in multiple aspects of cellular biology, including inflammatory processes. He compared plasma with cerebrospinal fluid samples in aging individuals, and found significant overlap between proteins that were altered as a function of age in both fluids. His group focused on one such protein, macrophage colony stimulating factor (MCSF). Interestingly, peripheral MCSF prevented memory impairment in APP transgenic mice, but left cerebral amyloid and neurogenesis unchanged in these animals. But what is the mechanism? To address this, his group targeted *cfms*, the gene encoding the MCSF receptor, by using the cre/loxP system to specifically delete *cfms* in neurons. These mice had profound neuropathology and increased sensitivity to kainic acid challenge – suggesting that MCSF–*cfms* interaction protects vulnerable neurons from excitotoxicity. He concluded by presenting recent evidence using a parabiosis technique – where the circulatory systems of two congenic mice are physically connected – in experiments designed to test whether systemic factors in young mice could be beneficial to brains of older animals. Strikingly, they noted a reduction of new neurons in young mice, but an increase in the older animals. Their focus is now squarely on the factors that may be responsible for these phenotypic changes, and they hypothesize that the chemokines CCL2 and CCL11 are playing pivotal roles in this context.

What are the best molecules to target beyond A β ?

So, if we accept that in order for treatment to be effective it must be initiated early on in the course of the disease, the next issue becomes: what are the best targets aside from A β ? Bart de Strooper (Center for Human Genetics, Leuven, Belgium) broached this issue by focusing on microRNAs (miRNAs) in the context of AD pathobiology. He opened by giving a brief overview of 18–23-mer miRNAs, which are unique in their ability to regulate more than one gene at a time, and in doing so act as fine-tuners of disease biology. The importance of the miRNA machinery in disease was highlighted by his group’s studies in *dicer* deficient mice. When *dicer*, the enzyme that processes miRNAs, is knocked out in the CNS, this leads to profound neurodegeneration. The mechanism seems to involve ERK1, which is increased in activity and mRNA abundance in these knockouts. miRNAs are also dysregulated in AD cases, and the 3’ untranslated region of APP contains miRNA-binding sites. Furthermore, APP seems to be regulated by miRNAs in cultured neurons, and this also seems to hold for β -site APP-cleaving enzyme (BACE)1. The families of miRNAs that seem to be most important in this context are the 29a/b-1 varieties. While de Strooper acknowledged that the work presented was

preliminary in nature, he concluded by proposing a multiple-hit model of AD pathogenesis where miRNAs are stochastically dysregulated.

Toward the middle of the meeting, all eyes were focused on boosting cAMP response element-binding (CREB) protein activity as a therapeutic target for AD. Sheena Josselyn (Hospital for Sick Children, ON, Canada) began the discussion by presenting data from CREB knockout mice, which have profound spatial memory impairment. Conversely, viral-mediated overexpression of CREB in the lateral amygdala rescues cognitive impairment in CREB knockouts. The immediate early gene *Arc* seems to be important in CREB's beneficial effects on memory, as its expression is correspondingly increased when CREB expression is forced in the mice. But what is the relevance of these findings to AD? To work this out, her group first examined CREB activity in the TgCRND8 mouse model of AD and found a deficit in CREB activation. To determine whether this result had functional implications in the context of AD, she then forced CREB expression in the dorsal hippocampus of TgCRND8 mice and rescued spatial memory deficit in this AD mouse model. Additional evidence of beneficial effect came when her group discovered that the CREB vector restored dendritic spines in TgCRND8 mice. The CREB theme was carried on by Ottavio Arancio (Columbia University, NY, USA), who took an electrophysiological approach to determining the function of this protein. He began by presenting evidence that A β impairs memory and also blunts phosphorylation of CREB. On the other hand, increasing CREB phosphorylation produces a beneficial effect on synaptic transmission. Strikingly, he showed that picomolar levels of A β actually enhance long-term potentiation (LTP) and memory, while the peptide in the nanomolar range inhibits LTP. Furthermore, his data indicate that depletion of A β impairs post-tetanic potentiation and LTP, which can be rescued by adding back picomolar levels of the peptide. Even more, the beneficial effects of picomolar A β on post-tetanic potentiation/LTP rely on the $\alpha 7$ nicotinic acetylcholine receptor. Finally, monomeric A β is not able to rescue the effect of A β depletion, suggesting a beneficial role of A β oligomers at low molarity.

Marc Tessier-Lavigne (Genentech, CA, USA) gave a presentation that unfolded like a good novel: full of plot twists and turns. He began by introducing death receptor (DR)6, a member of the TNF receptor/NGF receptor superfamily. His group was interested in DR6 given its role in regulating axonal growth, and its high protein expression pattern in embryonic neurons. He presented data showing that DR6.1 promotes degeneration of trophic factor-deprived neurons, while an antibody against the receptor is protective. He then deduced from trophic factor withdrawal experiments that a suicide ligand likely exists for DR6 – but what is the identity of this ligand? The answer was, shockingly, amino-terminal cleaved APP. He demonstrated this by a variety of removal and add-back approaches, and went on to link this receptor/ligand dyad to caspase-6-induced axonal degeneration. DR6 mutant mice showed less axonal die-back than wild-type mice, demonstrating that ablation of DR6 function can enhance neuronal regeneration *in vivo*. The plot thickened further when he showed that tau protein is actually downstream of amino-terminal cleaved APP, and is required for the inhibitory effect of the latter protein on axonal regeneration.

Stephen Strittmatter (Yale University, CT, USA) updated us on studies conducted in his lab related to Nogo receptor (NgR) and cellular prion protein (PrP^C). He began by showing that the NgR pathway plays a salient role in limiting CNS anatomical plasticity. This is important in the context of AD, because when NgR expression is forced in AD model mice, plaques double, and when NgR is inhibited, plaque load is reduced. He suggested that A β may physically interact with NgR and thereby impact NgR downstream signaling. He then showed *in vitro* data suggesting that A β oligomers bind neuronal processes. Using an *in vitro* A β neuronal binding assay, Strittmatter's group identified PrP^C as a binding protein for A β oligomers. To validate the functional significance of the A β oligomer–PrP^C interaction, they looked in primary neurons from PrP^C deficient mice, and found that A β binding was reduced

by approximately half. Furthermore, in the absence of PrP^C, A β -induced inhibition of LTP was relieved. Finally, A β was able to promote activation of the Src family kinase Fyn in a PrP^C-dependent fashion and PrP^C deletion was able to rescue early death, synaptotoxicity and hippocampus-dependent learning and memory deficits in AD model mice. These results suggest that small molecule inhibitors of A β binding to PrP^C may be effective therapeutics.

Autophagy, or cell 'self-eating' has become a hot topic in the field of AD research; however, there has been considerable debate over whether therapeutic approaches should boost or inhibit this pathway in AD. Zhenyu Yue (Mount Sinai School of Medicine, NY, USA) gave a thought-provoking presentation on the topic, and opened with a brief overview of autophagy in AD. Specifically, he stressed that autophagy is the only pathway whereby neurons can jettison long-lived proteins and organelles. He also described the autophagic process, including autophagosome formation, trafficking, fusion and lysosomal degradation. He hypothesized that aberrant induction of autophagy results in accumulation of autophagic vacuoles that contain A β and other proteins, and that impairment of this pathway likely contributes to AD pathogenesis. He even showed *in vivo* data demonstrating that impaired neuronal autophagy leads to inhibited clearance of abnormal tau protein. Yue concluded by stating that augmenting the autophagic machinery in AD represents an important emerging therapeutic target for the disease.

Toward the end of the meeting, JoAnne McLaurin (University of Toronto, ON, Canada) and Linda Van Eldik (University of Kentucky, KY, USA) presented novel small molecule AD therapeutic approaches. McLaurin focused on the naturally-occurring small molecule, scyllo-inositol. She opened with a phenotypic description of the TgCRND8 mouse model of AD, which her group is using as a preclinical system to evaluate the effects of scyllo-inositol. In these mice, the small molecule strikingly breaks down A β fibrils; reduces cerebral amyloidosis and brain inflammation; rescues septal cholinergic neurons and memory impairment; increases survival; increases synaptophysin immunoreactivity; and increases cholinergic proteins in hippocampal axons. Enticingly, scyllo-inositol has high CNS bioavailability, which is obviously a favorable pharmacologic profile in terms of a centrally acting AD treatment. Van Eldik presented a different strategy, and focused on two families of drugs: the Minokine family of p38 MAPK inhibitors, and the Minozac family, which were designed not to inhibit p38 MAPK, but to attenuate glial activation. Her group tested both families of small molecules in a mouse A β infusion model. In both cases, they found that the drugs inhibited brain cytokines, prevented synaptophysin loss and restored deficits in a Y-maze assay. Thus, these two new classes of anti-inflammatory drugs seem to mitigate AD-like pathology in a preclinical mouse model.

The 'mighty macrophage': a new cell type to target in AD?

The enigmatic mononuclear phagocyte has garnered increasing attention in the field of AD research owing to its ability to potentially engulf and clear A β . Richard Ransohoff (Cleveland Clinic, OH, USA) kicked off a session on 'Alzheimer's and the Immune System' by giving an overview of the roles played by microglia, monocytes and macrophages in AD pathobiology. He focused on fractalkine receptor, exclusively expressed by microglia in the CNS, which receives the signal from fractalkine, a cytokine-like molecule that is produced by neurons. This pathway seems to be used as a signaling molecule between microglia and neurons. Interestingly, when fractalkine receptor-deficient mice were intoxicated with MPTP to induce Parkinson's-like pathology, they suffered worse disease than wild-type animals, suggesting a neuroprotective role of fractalkine signaling. Furthermore, when human mutant tau transgenic mice were crossed with fractalkine receptor knockouts, his group noted hyperactivated microglia, increased p38 MAPK phosphorylation and worse tau pathology. A similar type of experiment, but utilizing mutant human APP transgenics instead of tau in the cross, resulted

in decreased cerebral amyloid pathology but increased microgliosis, yet fewer microglia per plaque. These results begged the question of how to tell whether a mononuclear phagocyte is an inflammatory cell. To get at this concept, Ransohoff's group established a new model for inflammatory monocytes, where they expressed red fluorescent protein under regulatory control of the C-C motif chemokine receptor 2 (*Ccr2*) promoter. They crossed these mice onto a fractalkine receptor knockout background and also crossed them with a fractalkine receptor GFP reporter line. Strikingly, after induction of experimental autoimmune encephalomyelitis (a mouse model for the human demyelinating disease multiple sclerosis), mononuclear phagocytes in these crossed mice expressed the fractalkine receptor, but not *Ccr2*. Furthermore, it seems as though monocytes are replaced by neutrophils in the experimental autoimmune encephalomyelitis model, and that *Ccr2* is necessary for monocytes to infiltrate into the brain.

Joseph El Khoury (Massachusetts General Hospital, MA, USA) presented data involving both *Ccr2* and fractalkine receptor that were largely in agreement with Ransohoff's. He opened by giving a recap of the roles played by the 'mighty macrophage' in the periphery and in the CNS. He showed data that mononuclear phagocytes do indeed accumulate in AD patients' brains, and posed the question of what happens if one interferes with this process. Using irradiation chimera approaches, he demonstrated that the BBB was compromised, which allowed bone marrow-derived mononuclear phagocytes to populate the CNS. Furthermore, utilizing a similar approach in doubly transgenic mutant PS1/APP mice, El Khoury observed infiltrating mononuclear phagocytes around amyloid plaques. He was able to confirm this by physically connecting the circulatory systems of two mice using parabiosis. Similar to Ransohoff's observations, he found that this effect requires the fractalkine receptor. El Khoury moved on to cross *Ccr2*-deficient mice with the Tg2576 mouse model of AD. He noted reduced CD11b⁺ macrophages near plaques but increased A β deposition in brain parenchyma and around cerebral vessels in *Ccr2*-deficient Tg2576 mice. He then crossed fractalkine receptor knockout mice with double transgenic PS1/APP animals and noted reduction in cerebral amyloid, improvement in behavioral deficits, slowed association of mononuclear phagocytes with A β deposits and increased expression of granulocyte-macrophage colony stimulating factor. El Khoury concluded by showing that microglia from mutant human APP transgenic mice have increased proinflammatory cytokine production, but are defective A β phagocytes. When taken together with Ransohoff's findings, El Khoury's data suggest that mononuclear phagocytes are capable of restricting cerebral amyloid.

Josef Priller (Charité – Universitätsmedizin Berlin, Germany) delved more deeply into the use of irradiation bone marrow chimeras to answer questions related to the provenance and function of mononuclear phagocytes in AD mouse models. Specifically, his group utilized mice expressing green fluorescent protein under the ubiquitous chicken β -*actin* promoter as peripheral mononuclear phagocyte donors, and wild-type or genetically engineered mice as recipients. He showed that brain engraftment of these cells is markedly increased after facial axotomy injury. Similar to Ransohoff's and El Khoury's data, Priller showed that *Ccr2* is required for brain recruitment and engraftment of these adoptively transferred cells, and that *Ccr2* deficiency accelerates progression of AD-like pathology in transgenic mice. Interestingly, use of a head shield dramatically reduces engraftment efficiency, showing that irradiation is needed to sensitize the CNS to accept the engrafted cells. Finally, his group conducted an experiment in Tg2576 mice, where the independent variable was unprotected irradiation or head-sparing irradiation. Interestingly, in the former scenario, engrafted cells were farther away from the plaque and were morphologically different from macrophages in the latter condition. While there were no gross changes between these two conditions on amyloid load, biochemical assay for insoluble A β revealed increased abundance in the unprotected irradiation group.

In my talk, I focused on multiple strategies to impact mononuclear phagocytes, and the functional implications of these different approaches in the context of AD-like pathology. In

the first scenario, I presented data on blocking TGF- β receptor type II signaling using mice that express a dominant-negative form of this receptor under regulatory control of the innate immune CD11c promoter (CD11c-DNR mice). When these mice were crossed with the Tg2576 mouse model of AD, aged bigenic animals manifested remediation of behavioral impairment in open field and Y-maze assays; reduction in brain parenchymal and cerebrovascular A β deposits; increased infiltration of CD45^{hi}CD11b⁺CD11c⁺Ly-6C⁺ mononuclear phagocytes from the periphery into the brain; and increased brain IL-10 mRNA abundance. Furthermore, aged CD11c-DNR $\times$ APPPS1 mice demonstrated approximately seven- to eight-fold increased numbers of brain-infiltrating mononuclear phagocytes by flow cytometry. *In vitro* studies showed that CD11c-DNR peripheral macrophages had approximately threefold increased capacity for A β phagocytosis, and pharmacologic inhibition of the type I TGF- β receptor, ALK5, in wild-type peripheral macrophages produced a similar effect on A β uptake. Thus, it seems that relieving TGF- β inhibition promotes entry of A β -clearing peripheral macrophages into brains of mice with AD-like pathology. I moved on to consider the proinflammatory molecule S100B, which is produced by reactive astroglia after neuronal insult and in AD patient brains. To elucidate the role of this molecule in AD-like pathology, we crossed mice expressing human *S100B* under endogenous regulatory control with Tg2576 mice. Bitransgenic mice manifested exacerbated astrogliosis and microgliosis burden and elevated levels of proinflammatory innate cytokines in brain that preceded increased size and abundance of A β plaques. In addition, human S100B expression drives amyloidogenic APP processing, providing a link between neuroinflammation and A β production. When taken together, these data highlight that there are multiple forms of innate immune activation, some of which are beneficial in the context of AD pathology, and others, deleterious.

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