Emma RANGER

Mouse as a model for Alzheimer diseases

Model organisms in molecular biology

To address this topic, I studied the article « Alzheimer's Disease: Experimental Models and Reality » by Eleanor Drummond and Thomas Wisniewski from the Department of Neurology and the department of Pathology and Psychiatry, Alexandria at NYU School of Medicine. It was published in February 2017 in Acta Neuropathol journal.

First, I will introduce the Alzheimer disease, it causes and symptoms, then I will present the models allowing studies on Alzheimer disease and concentrate my explanation on mice. Finally, I will explain the limits of mice as models for Alzheimer disease and how science can progress.

I. Alzheimer's disease

I.1 Causes

Alzheimer's disease is a complex, multi-factorial disease, and one that appears to be unique to humans. AD is defined in the brain by pathological accumulation of amyloid β (Aβ) which is a cleavage product of amyloid precursor protein (APP). In AD, Aβ accumulates into extracellular plaques in the brain parenchyma and in the vasculature (known as congophilic amyloid angiopathy), AD is also characterized by an abnormally accumulation of phosphorylated tau intraneuronally forming neurofibrillary tangles (NFTs). Neurofibrillary tangles consist mainly of intracellular tau protein, a microtubule-binding protein that, in AD, misfolds, becomes abnormally phosphorylated, and aggregates into skeins of filamentous material. Pathological aggregation of Aβ and phosphorylated tau occurs in a sequential process, small numbers of monomers first aggregate into oligomers intraneuronally, which then continue to aggregate into the fibrils observed in amyloid plaques and NFTs. It is supposed that oligomers are the most neurotoxic species in AD as levels of these species correlate much better with cognitive symptoms than presence of plaques or NFTs. Amyloid plaques primarily consist of aggregated Aβ. The most abundant forms of Aβ are Aβ1–40 and Aβ1– 42, but other important Aβ species include Aβ1–38, Aβ1–43 and Aβ with post-translational modifications such as AβN3pE (N-terminally truncated Aβ with a pyroglutamate modification), pAβ (Aβ with phosphorylated serine at position 8 or 26) and Aβ5-x (N- terminally truncated Aβ)[144]. The presence and amount of these different Aβ species is important because each species has a different rate of aggregation and they preferentially form different aggregated

species, some more toxic than others. For example pAβ has been shown to promote oligomer formation and propagation. There are two forms of AD: familial Alzheimer's disease (FAD) and sporadic Alzheimer disease (sAD). FAD is characterized by production of more aggregation prone species of Aβ, it is a rare form of Alzheimer's that is entirely passed down through genetics, being inherited from a parent.

I.2 Symptoms

The primary clinical manifestation of AD is severe and progressive cognitive decline. But AD has multiple symptoms, some are more frequent than others, the most important one is memory loss that disrupt the daily life of the patients. Other symptoms are: difficulty to accomplish daily acts, time and space confusion but also problems of oral and written expression. For now, AD can only be diagnosed with reasonable certainty via the postmortem examination of the brain for the characteristic lesions in patients with dementia.

II. Models of AD study

II.1 Different models used to study AD

Animals have allow studies of many diseases in physiological conditions. They also have enable to look into the development and process of pathologies in living organisms. Several species have been essential for countless advances. For instance, in 1885, Louis Pasteur has design rabies vaccines thanks to dogs and rabbits. In the 1980, research to find HIV treatment were done on rats and monkeys. For Alzheimer disease, the species with the most well characterized neuropathological features are non-human primates. To promote a greater understanding of the neurobiological substrates of AD, and to investigate the role of age in the pathogenic process, many investigators have employed nonhuman primates as a comparator. The advantages of using non-human primates to model AD include their biological proximity to humans, behavioral complexity, large brains that are favorable for imaging studies or CSF collection and a natural production and accumulation in parenchymal senile plaques and within the cerebral vasculature of Aβ that has 100% sequence homology with human Aβ. The majority of studies have used rhesus monkeys, they are used especially in behavioral and biomedical research, and much is known about the physiology and pathology of aging in these species.. Again, there is 100% sequence homology between human and rhesus monkey Aβ. Aβ levels accumulate with age, reaching similar levels in the cortex to that observed in human AD. AD associated neuropathology has also been characterized in grey mouse lemurs, which have also been used AD preclinical trials. Other species can also develop AD

associated pathology with age, the most known examples are dogs and the guinea pig relative Octodon degu. Other models have included invertebrate animals such as Drosophila melanogaster (fly) and Caenorhabditis elegans (worm), as well as other vertebrates such as zebrafish; however, given these models' greater distance from human physiology they are less extensively used.

II.2 Why mouse as a model ?

Mice and rats are the most used animals for tests and studies of human's health. In fact, genetically, mice are very similar to humans: 99% of their genes have an homologous gene present in humans. Moreover they possess a lot of benefits for laboratory farm: numerous descendants, fast development and a small size. Different linears are used in laboratory: BALB/c, C57BL/6,… These mice can also be subject to transformation…

II.3 Transgenic mice as models for AD

As we said earlier, AD is characterized by aggregation of Aß that is synthesize from amyloid precursor protein (APP is cleaved). Wild type mice present a different sequence of Aß than human. Indeed, 3 amino acids within the Aβ sequence are different in both human and wild type mice. These differences damage Aβ aggregation and stop the formation of amyloid plaques in wild-type mice. Without aggregation of Aß and so formation of amyloid plaques, AD studies can not be done. So, for AD to be correctly studied, mice must endure transgenic transformation. Transgenic process consists in introduction of DNA from one specie in another one. Thereby, the development of transgenic models offered much promise about the understanding of AD pathogenesis, allowing questions to be answered that were previously impossible to examine in humans. Initial transgenic models that express wild-type human APP in mice are not sufficient to study AD. In fact, it has been demonstrated that increased Aβ production is not enough to consistently show extensive AD associated neuropathology. But expression of human APP containing mutations associated with FAD resulted in consistent plaque pathology and varying amounts of consequent downstream AD-associated pathological features.

III. Limits and challenges

III.1 Limites

There are many available models of AD pathology, each with their own benefits and limitations. Results given from experimental models can be very informative about a number of specific aspects

of AD if researchers are aware of the limitations associated with each model. Even if mice are very appropriate models for AD studies, they also present disadvantages. First, researchers must consider that mice can contain endogenous rodent proteins and/or protein pathways that might react differently in response to non-physiological expression of specific human proteins and as such, downstream effects cannot be assumed to also occur in humans. Endogenous species differences between rodents and humans affect the cleavage and biochemistry of human Aβ in transgenic rodents. That could lead to amyloid clearing drugs working much better in transgenic mice than humans. Apparently, species differences also appear to influence Aβ biochemistry and deposition in physiological models. Therefore, it is important to well select species models for AD study. Furthermore, the most prevalent symptom of AD in humans is cognitive impairment. While the majority of animal models show some degree of cognitive impairment, the type and the timing of this impairment must be carefully considered, particularly in preclinical studies. An important question must then be answered: Is the process that mediates cognitive impairment in transgenic animal models the same as the one that mediates cognitive impairment in humans ?

III.2 How can science progress ?

Transgenic animal models represent partial models of FAD and not sAD. Much more research in humans must be done to determine the similarities and differences between FAD and sAD. Today, the lack of translation between preclinical studies and human studies must be solved. At the origin of this lack, we find inherent differences between FAD and sAD. It is then suggested that potentially these therapeutics that worked very well in preclinical studies could be better translated in clinical trials of FAD patients. If this is the case, then it will be essential to develop new models that are more representative of sAD, so that the effect of novel therapeutics in sAD can be tested more accurately. In additions, genetic studies have identified multiple loci that convey increased risk for sAD. It will be important for future studies to determine how these genetic risk factors contribute to AD associated pathology, and whether this is replicated in animal models of the disease.

IV. Conclusion

Animal models have the obvious advantage of providing the option to do preclinical testing in vivo, allowing the testing of general toxicity of new therapeutics and providing a system in which cognitive testing can be done. Careful examination of neuropathology and cognitive impairment in multiple species, including those closest to humans, shows that AD is a uniquely human disease. The best experiment is to perform research using human tissue whenever possible. The consistent lack of translation between animal models and human studies has resulted in the development of

more human-centric approaches. Many of these approaches are still being developed and fully characterized, however they offer great potential. Non-human primates offer the unique advantages of greater genetic similarity to humans and a more physiological relevant development of pathology that better resembles that in found in sAD compared to transgenic models, but studies are limited by availability, costs, time until onset of phenotype and the inconsistent presence of pathology in all animals. Going forward it will be necessary to perform preclinical testing in multiple animal models that each exemplifies a unique aspect of AD pathology, until a more complete and physiological animal model of sAD is available to ensure greater translation of preclinical results to human clinical trials.