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COMMENTARY

In vitro geroscience. Screening anti-aging drug combinations for neurodegenerative diseases

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Abstract

Geroscience is based on the concept that therapeutic approaches that work for aging will also work for age-related diseases, including neurodegenerative diseases such as Alzheimer's disease (AD). Single drugs have been ineffective in treating AD, so it seems reasonable to consider using multiple drugs in combination (cocktails) for a more effective treatment approach. However, initial screening of drug cocktails in animal models is costly and time-consuming. The human neuroblastoma cell line SH-SY5Y has neuronal properties and can be stressed with chemicals or transfected with adeno-associated virus (AAV) Aβ and/or pTau vectors for an in vitro model of neurotoxicity. Drug cocktails can then be easily screened for intervention efficacy compared to each individual drug in the cocktail.

Keywords: Drug cocktails, anti-aging drugs, geroscience, neuroblastoma cell line, Alzheimer's disease

Alzheimer's disease (AD) is a common neurodegenerative disease for which no single drug therapy has been successful. The concept of geroscience is that therapeutic approaches that work for aging will also work for age-related diseases, including AD. Therefore, rather than focusing on testing a single drug, it seems reasonable to consider using multiple drugs in combination (a cocktail) for a more effective treatment strategy. However, testing drug cocktails in animal models is expensive and time-consuming.

A simple and inexpensive system is needed. In this regard, Mairuae *et al*. recently published an article describing the use of a human neuroblastoma cell line to test the ability of a combination of mulberry fruit and leaf extracts to prevent hydrogen peroxide-induced cytotoxicity [1]. They showed that the protective effect was most pronounced with the extract combination compared to each individual extract, suggesting an interaction between the two extracts and that the extract combination hit a broader pathway of cellular targets.

Their observation reinforces the critical importance of using drug combinations to treat AD. However, this type of approach has not received the attention it deserves, mainly because there is still a mystery as to what causes AD, and in fact there are most likely are multiple causes. The mainstream thinking is that using drug combinations to treat AD is a shotgun approach and not scientifically sound. This is counterintuitive to the geroscience concept, which is based on the underlying principle that if a drug cocktail is effective in delaying aging, then it will be effective in delaying the dementia and neuropathology associated with AD. Our laboratory has recently shown that a combination of rapamycin, acarbose, and phenylbutyrate is effective in enhancing resilience to aging in C57BL/6 and HET3 mice [2]. We also showed that the drug combination delayed the onset of age-related cognitive impairment [3], suggesting that it would be a promising combination to test for delaying or preventing AD.

Part of the reluctance to embrace drug combinations for the treatment of AD may be the high cost and intensive effort required to conduct such studies in animal models. An *in vitro* cell culture system would be ideal for screening drug combinations in a cost-effective and timely manner, as described by Mairuae *et al*. [1]. They used the SH-SY5Y human neuroblastoma cell line, which is of neuronal origin and exhibits neuronal cell properties including cytotoxicity influence. To use this cell line to screen drug combinations for AD, we performed transfections with adeno-associated virus (AAV) vectors containing sequences for Aβ42 and pTau. Drugs that are soluble in aqueous solutions, such as peptides, are easily tested in this model system. However, many insoluble drugs can be solubilized in solvents such as DMSO and still be tested

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under the right conditions. Since we are not looking for a specific target, there is no need to use a reporter system. Instead, we have developed a streamlined immunohistochemistry format with multiple neuropathological markers as readouts to measure the efficacy of the drug cocktail compared to each individual drug.

In conclusion, the use of the SH-SY5Y neuroblastoma cell line is an example of a viable, robust and inexpensive *in vitro* system for screening anti-aging drug cocktails as effective therapeutics for neuronal cell damage associated with neurodegenerative conditions such as AD. By testing different combinations of drugs targeting a wider range of aging pathways, it will be possible to screen candidate drug cocktails quickly and efficiently, justifying the time and expense of larger-scale animal studies.

Declarations

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