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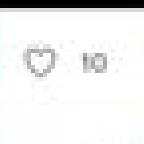
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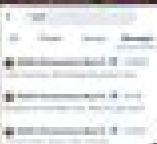
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R Sandford

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The Propagation of Neurodegenerative Diseases by Inflammation and

Exosomes Valerie Sackmann, 2019-10-16 Alzheimer's disease AD and Parkinson's disease PD are the two most common neurodegenerative diseases with rates increasing along with the ageing global population. Despite best efforts we still do not understand the etiopathogenesis of these diseases and there are no effective disease modifying treatments. Cognitive deficiencies or motor complications that emerge during AD and PD are thought to be the result of the accumulation of misfolded aggregate prone proteins such as amyloid A and tau or synuclein syn respectively. Growing evidence suggests that prefibrillar oligomers of A and syn oA and o syn are key contributors to the progression of these diseases. The progressive accumulation of these proteins leads to a gradual spread of pathology throughout interconnected brain regions but the mechanisms by which this spreading occurs are still largely unknown. Neuroinflammation has been recognised as an important contributor to neurodegenerative disease. It is hypothesised that a pro inflammatory environment initiated by the innate immune system either through activation from A itself or indirectly through neuronal injury signals in AD. These phenomena are thought to either cause or accelerate AD such that an anti inflammatory approach may be neuroprotective. In paper I we investigated whether different inflammatory environments affected the transfer of oA between neuron like cells in addition to investigating inter and intracellular protein changes. This study demonstrated that an anti inflammatory environment reduces the transfer of oA between cells. We also provide evidence that these cells begin to take on the phenotype of the inflammatory milieu while also demonstrating that the expression profile of endosomal lysosomal and protein trafficking proteins is altered during these conditions. Small extracellular vesicles called exosomes which are key players in cell to cell communication have been proposed to play an influential role in spreading neurodegenerative proteins between cells. Exosomes are small membranous vesicles that are formed by the inward budding of multivesicular bodies (MVBs). These MVBs can then merge with the plasma membrane to be released into the extracellular environment as vesicles which serve as vehicles for transferring proteins, lipids and mRNAs between cells. The ESCRT dependent pathway is the most understood mechanism underlying exosome biogenesis. However, exosomes can also be formed through ESCRT independent pathways including through the hydrolysis of sphingomyelin by neutral sphingomyelinase 2 (nSMase2) which produces ceramide. Paper II investigated whether exosomes formed through an ESCRT independent pathway plays a significant role in the transfer of o syn between neuron like cells. As oxidative stress is a common feature in PD brains which in turn dysregulates nSMase2 activity we also tested our model under hypoxic conditions. Inhibition of nSMase2 significantly reduced the transfer of o syn between cells but also resulted in decreased syn aggregation. Hypoxia did not influence o syn transfer however it significantly dysregulated the sphingolipid composition which may be important for syn binding to exosomes and exosome communication. During AD and PD there is a noted reduction in the effectiveness of autophagy a

process critical to cellular proteostasis Recent studies have uncovered shared regulatory mechanisms of exosome biogenesis and autophagy suggesting that they are closely linked Previous findings have shown that inhibition of autophagy in AD mice mediates A trafficking through altering the secretion of A in MVBs To further study this effect we investigated the interplay between autophagy and exosome secretion using ATG7 knock out x APPNL F knock in AD mice in paper III These autophagy deficient AD mice had a reduced extracellular A plaque load but increased intracellular A which was found to be assembled into higher ordered assemblies While exosomal secretion was dysregulated in these mice the amount of A packaged into the exosomes was unchanged Lastly one of the biggest challenges in developing effective treatments for AD is the lack of early diagnosis of living patients As the connection between exosomes and the spread of neurodegenerative proteins is still relatively new there remains a diagnostic potential to be explored with exosomes Paper IV aimed to develop a new diagnostic assay to detect oA in exosomes isolated from human cerebrospinal fluid Although exosomal oA was readily detected in some of these samples the assay's sensitivity requires additional optimisation before it can be further validated for the clinic In summary the studies presented in this thesis have furthered our understanding of how inflammation autophagy and exosomes contribute to the intercellular transmission of AD and PD associated proteins We have shown that an anti inflammatory approach may slow down the progression of AD through reducing the transfer of oA between cells We also provide novel findings relating to the biogenesis of exosomes which in turn affected the ability of exosomes to transmit neurodegenerative proteins between cells and their association with autophagic processes Finally we have investigated the feasibility of exosomes as an early AD diagnostic marker This work has helped to elucidate some of the mechanisms underlying the progression of neurodegenerative diseases which may be useful targets for the investigation of new therapeutic avenues

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web the black sun german schwarze sonne is a type of sun wheel german sonnenrad symbol originating in nazi germany and later employed by neo nazis and other far right individuals and groups the symbol's design consists of twelve radial sig runes similar to the symbols employed by the ss in their logo

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web the term black sun german schwarze sonne also referred to as the sonnenrad the german for sun wheel is a symbol of esoteric or occult significance notable for its usage in nazi mysticism today it may also be used in occult currents of germanic neopaganism and in irminenschaft or armanenschaft inspired esotericism

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web oct 13 2020 40 373 ratings7 698 reviews goodreads choice award nominee for best fantasy 2020 the first book in the between earth and sky trilogy inspired by the civilizations of the pre columbian americas and woven into a tale of celestial prophecies political intrigue and forbidden magic a god will return

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pictographic representation of the sun in ancient norse paganism similar symbols

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web between earth and sky novel series between earth and sky is a fantasy novel series by american writer rebecca roanhorse it currently comprises two novels black sun 2020 and fevered star 2022 2 it is an epic fantasy series inspired by various pre columbian american cultures

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web black sun twining novel a 2005 novel by james twining black sun manga a manga first published in 2007 written and illustrated by uki ogasawara black sun roanhorse novel a 2020 fantasy novel by rebecca roanhorse black

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web neo nazi symbols alternate names sunwheel black sun the sonnenrad or sunwheel is one of a number of ancient european symbols appropriated by the nazis in their attempt to invent an idealized aryan norse heritage

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web black sun during the clone wars the focus of the jedi knights on defeating the separatists meant a decline of law enforcement particularly in the sparsely patrolled outer rim territories this allowed criminal elements

the black sun sonnenrad symbol learn religions - Sep 20 2023

web jan 24 2019 by catherine beyer updated on january 24 2019 the black sun also known as the sonnenrad sun wheel in german specifically comes from the floor of the north tower of wewelsburg castle which was renovated by ss leader heinrich

himmler

black sun goodrick clarke book wikipedia - Feb 13 2023

web black sun aryan cults esoteric nazism and the politics of identity is a book by the historian nicholas goodrick clarke in which the author examines post war nazi occultism and similar phenomena it was published by new york university press in august 2001 isbn 978 0814733264 and reissued in paperback isbn 0 8147 3155 4