Review

Peptidylarginine Deiminases—Roles in Cancer and Neurodegeneration and Possible Avenues for Therapeutic Intervention via Modulation of Exosome and Microvesicle (EMV) Release?

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Abstract: Exosomes and microvesicles (EMVs) are lipid bilayer-enclosed structures released from cells and participate in cell-to-cell communication via transport of biological molecules. EMVs play important roles in various pathologies, including cancer and neurodegeneration. The regulation of EMV biogenesis is thus of great importance and novel ways for manipulating their release from cells have recently been highlighted. One of the pathways involved in EMV shedding is driven by peptidylarginine deiminase (PAD) mediated post-translational protein deimination, which is calcium-dependent and affects cytoskeletal rearrangement amongst other things. Increased PAD expression is observed in various cancers and neurodegeneration and may contribute to increased EMV shedding and disease progression. Here, we review the roles of PADs and EMVs in cancer and neurodegeneration.

Keywords: extracellular vesicles (EVs); microvesicles (MVs); exosomes; peptidylarginine deiminases (PADs); deimination; Chlor-amidine (Cl-Am); cancer; neurodegeneration; cytoskeleton; induced pluripotent stem cells (iPSCs); histone H3; epigenetics

1. Introduction

Exosomes and microvesicles (EMVs) play physiological roles as mediators of intercellular communication, transferring molecules characteristic of their parental cells such as receptors, enzymes, cytokines, growth factors, and genetic material—including miRNAs—to recipient cells thus affecting diverse processes such as differentiation, migration, and angiogenesis [1–4]. As EMVs are present in body fluids including blood, urine, and cerebrospinal fluid, they may serve as reliable biomarkers of pathophysiological processes [5–9].
Microvesicles (MVs), are 100–1000 nm sized phospholipid-rich vesicles that are released from the cell membrane of diverse cell types as part of normal cell physiology [10,11] and upon stimulation, with for example growth factors or cytokines, and/or in early apoptosis or [5,7]. MV release depends on calcium ion influx, which occurs either through pores created by sublytic complement or stimulation of calcium channels, such as P2X$_7$, or calcium released by the endoplasmic reticulum through various calcium channels on activated cells [3,12]. MVs can also be released during pseudoapoptotic events [13]. The increase in cytosolic calcium results in cytoskeletal reorganization which is facilitated by the activation of various enzymes, including calpain, gelsolin, and scramblase; protein kinase ROCK-1 (Rho associated kinase 1) and the simultaneous inhibition of translocase and phosphatases [14]. Subsequent loss of membrane asymmetry and membrane blebbing leads to MV formation and release [6,15].

Exosomes are smaller than MVs, 30–100 nm in size, are generated intracellularly, and released into the lumen of an endosome that becomes a multivesicular body which then is exocytosed, releasing its cargo of exosomes at the plasma membrane [12,16,17]. Cellular components crucial for exosome formation include components of ESCRT, which are involved in the formation of multivesicular bodies (MVBs) and intraluminal vesicles [18,19]; syntetin and syndecan [20]; sphingolipid ceramide and tetraspanins [21]. Exosome secretion can also be modulated by microenvironmental pH [22]. During the final step of exosome release, the multivesicular bodies fuse with the plasma membrane, mediated by membrane-bridging SNARE complex machinery [23], which has been reported to participate in the fusion between MVBs with the plasma membrane and exosomal release into the extracellular medium [24]. In addition to EMVs, larger vesicles (>1 µm) are released from cells as apoptotic bodies [25].

As EMVs have been shown to actively contribute to the progression of numerous pathologies—including cancers [10,26–28] and autoimmune [29,30] and neurodegenerative [8,31–33] diseases—they pose as therapeutic targets in treatment of disease. Unravelling mechanistic pathways involved in EMV biogenesis may thus provide avenues for selective interception of EMV release [5,7]. Recent discoveries have elucidated roles for peptidylarginine deiminases (PADs) and their pharmacological inhibition in EMV shedding [26,34]. The PADs are a family of five tissue specific calcium activated enzymes that cause irreversible changes of protein-bound arginines into citrullines [35,36], resulting in protein misfolding and functional changes in target proteins [36–38]. While PADs play physiological roles [39], their dysregulation is detected in various pathologies [40–44]. Pharmacological PAD-inhibition has shown promising results in cancer models both in vitro [45,46] and in vivo [43,47], as well as in animal models of various autoimmune diseases [48–52], neuronal injury [53], hypoxia [54], and atherosclerosis [55].

2. Exosomes and Microvesicles EMVs in Cancer

Cumulative evidence implicates EMVs in the pathogenesis of cancer, either directly or indirectly. Elevated EMV levels in the blood from cancer patients has been demonstrated by various investigators and been shown to aid tumour spread and survival [56–58]. EMV shedding from cancer cells can contribute to their resistance to chemotherapeutic agents and has been shown to increase active drug efflux. In addition, chemotherapeutic drugs have been shown to stimulate cells to release EMVs, which have been shown to carry the drugs within them [22,59–66]. It has been shown that inhibition of EMV release can effectively increase drug retention within cancer cells and render them more susceptible to anticancer drug treatment [22,27,60–62] as well as reducing the dose of docetaxel required to limit tumor growth in vivo [59].

3. Peptidylarginine Deiminases PADs in Cancer

PAD dysregulation is elevated in numerous malignant tumours and associated with cancer progression. Overexpression of PAD2 and PAD4 isozymes has been reported in patients’ blood and tissues [67–71].

PAD4 is the only isozyme that contains a classic nuclear localisation signal [72,73] and acts as a transcriptional co-regulator for various factors including p53, p300, p21, and ELK1 and via deimination of
the N-terminal tails of various histone proteins [74–76]. PAD4 plays a role in apoptosis as it regulates p53 gene activity during DNA damage by acting as a co-mediator of gene transcription and epigenetic cross talk with histone deacetylase 2 (HDAC2) [77]. PAD4 is also co-localised with cytokeratin (CK), an established tumour marker which occurs in various isoforms, some of which are deiminated. The deiminated CK isoforms become resistant to caspase-mediated cleavage, contributing to the disruption of apoptosis in cancer tumours [68]. PAD4 also acts as a cofactor in epidermal growth factor-mediated target gene activity, activating the expression of proto-oncogene c-fos [76], interacting with p53 and influencing the expression of its target genes [74,75,78,79]. PAD4 is also linked with oestrogen receptor target gene activity via histone tail deimination [80]. In gastric carcinoma, PAD4 upregulates C-X-C chemokine receptor 2 (CXCR2), keratin 14 (KRT14) and tumour necrosis factor-α (TNF-α) expression levels [81].

Both PAD2 and PAD3 have also been localized and detected in the nucleus in spite of lacking a classic nuclear translocation site such as is found in PAD4 [54,70,82]. In cancer cells, PAD2, which is the most widely expressed isozyme in the body [35], has been shown to deiminate histone H3 and play a role in gene regulation [43,70,83,84]. Recent studies are increasingly identifying multifactorial roles for PAD2 and PAD4 in cancer pathologies, depending on tumour type [71,85–88]. In gastric cancer, the PADI2 gene was found to advance abnormal cell behaviour by increasing expression levels of CXCR2, a cell proliferation and invasion gene; while PADI2 has deleterious effects on tumour growth and metastasis in liver tumour cells via regulation of the tumour growth gene erythropoietin (EPO) [71]. Colon cancer has, on the other hand, been associated with downregulation of PADI2 [86,87], while PADI2 affects differentiation of normal colon and can suppress proliferation of colonic epithelial cells through protein deimination [86,87], accompanied by arrest of cell cycle progression in G1 phase [86]. In colon cancer cells (HCT116), PAD-inhibitor Cl-amidine induces the upregulation of several tumor suppressor microRNAs, which are otherwise downregulated in cancers [89]. In breast cancer (MCF-7 cells), inhibiting PADI2 expression significantly decreased cell migration ability but did not affect cell proliferation and apoptosis [85]. PAD4 has also been shown to negatively regulate tumor invasiveness in breast cancer models both in vitro and in vivo via citrullination of glycogen synthase kinase-3β (GSK3β) [88]. Overall, these findings emphasize the need for further testing of PAD isozyme selective inhibitors for intervention in cancer, alone or in combination, with regard to tumour type.

4. The Interplay of PADs and EMVs in Cancer

The presence of PADs has been confirmed in EMVs released from various cancers cells [90]. Based on a search in the Vesiclepedia dataset (http://www.microvesicles.org/), using gene symbol identifiers, PADs have been reported in EMVs from melanoma, breast, colon, kidney, lung, melanoma, ovarian, and prostate cancer cell lines [90], as well as colorectal cancer cells [91]. It may be postulated that the increased EMV release observed in cancers is partly driven by elevated PAD expression in cancers and that PAD enzymes—which are amongst the cargo packaged in EMVs—are carried into plasma where they can deiminate target proteins [92]; and aid in the spread of cancer indirectly.

In metastatic prostate PC3 cancer cells, both PAD2 and PAD4 isozymes were found to be elevated and to undergo increased nuclear translocation in correlation with increased EMV release [26].

Both PAD2 and PAD4 have been shown to translocate to the nucleus in response to TNFα upregulation [93–95]. As part of the inflammatory response, it may be postulated that increased EMV release also causes upregulation of TNFα which may lead to a feed-back loop of PAD translocation and EMV shedding in an ongoing inflammatory environment.

Which of the PAD isozymes is the main player in EMV release and the critical respective target proteins for successful MV and/or exosome shedding has to be further investigated. The different PADs may well be either selectively or collectively involved with different, albeit equally important, roles. In addition, the specific effect of PAD isozymes involved in EMV biogenesis will need to be taken into consideration dependent on tumour type. The selectivity of potential EMV inhibitors and combinatorial application with chemotherapeutic agents is thus of great interest. Most potential EMV inhibitors tested so far have displayed a preferential tendency for inhibition of either MVs or
exosomes [22,34,59,61,96–98] and thus the effect of PAD inhibitor Cl-amidine observed on both vesicle types indicates their potential usefulness. A combination of selective EMV inhibitors may indeed encourage re-testing of chemotherapeutic drugs currently not in favour due to severe side effects and poor effectiveness, as for example 5-FU treatment of prostate cancer [99].

5. Deiminated Target Proteins and PAD-Interacting Proteins Identified in EMV Biogenesis

Depending on target protein preference of PAD2 and PAD4, EMV release may occur via cytoskeletal and/or epigenetic pathways as the different PAD isoforms have indeed demonstrated distinct substrate preferences, with PAD4 showing more restrictive substrate specificity compared to PAD2 [100–103]. While PAD4 prefers sequences with highly disordered conformation, PAD2 has a broader sequence specificity, which might partly be reflected by the broader tissue expression of PAD2 [104]. PAD2 deiminites β- and γ-actins [100] and has been shown to affect histone H3 deimination [84], while PAD4 has been shown to deiminate histone H3 and H4 [104,105] and to regulate histone arginine methylation levels [80].

Targets of PAD-activation observed in EMV release include cytoskeletal actin which contributes to the reorganisation of the cytoskeleton necessary for successful vesicle release [15]. The presence of deiminated β-actin increased in cells that were stimulated for EMV release was markedly diminished after pre-treatment with PAD-inhibitor [26]. β-Actin, one of six different human actin isoforms, is a cytoskeletal protein involved in cell structure and integrity, cell migration, and movement [106]. This provides evidence for the importance of PAD-mediated deimination of target proteins that are involved in cytoskeletal rearrangement—such as β-actin, actin α1, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH)—as an essential step for successful EMV biogenesis as the process of multivesicular body recruitment to the plasma membrane to release exosomal cargo likely involves actin and microtubular elements of the cytoskeleton [107]. During vesicle formation, both β- and F-actin stress fibres play important roles in the redistribution of the actin-cytoskeleton through the activation of Rho/Rho-associated kinase (ROCK) pathways during apoptosis and thrombin stimulation [14]. Deiminated β- and γ-actins have indeed also previously been detected in sera and synovial fluid from RA patients [108] and been identified as a substrate for PAD2 in ionomycin-activated neutrophils [100]. Other deiminated protein targets identified in association with EMV release included GAPDH, which is reported to be exosome associated ([109] http://www.exocarta.org). It is a multifunctional enzyme involved in glycolysis, nuclear functions such as transcription and DNA replication, as well as apoptosis [110]. GAPDH has also been shown to contribute to the regulation of intracellular Ca$^{2+}$ levels via binding to integral membrane proteins, such as the inositol-1,4,5-triphosphate receptor (IP3R) and sarcoplasmic reticulum Ca$^{2+}$ (SERCA) pump [111,112]. Cytosolic GAPDH also catalyzes microtubule formation and polymerization by binding the cytoskeletal protein tubulin [113] and is associated with endoplasmic reticulum (ER) to Golgi vesicular transport [114]. Based on a STRING analysis (https://string-db.org/), putative binding partners of PAD2 and PAD4 were identified and found to be present in EMVs based on a search by gene symbol in the Vesiclepedia protein data set (Figure 1). These included histone H3, known to be deiminated [84,104,105,115]; p53, which is known to be regulated by PAD4 [74,116]; interleukin 6 (IL6), one of the major cytokines in the tumour microenvironment [117]; epidermal growth factor (EGF) which is a crucial mitogenic factor including in prostate cancer [118]; Tripartite Motif Containing (TRIM) 9 and TRIM 67 which are associated to microtubule binding [119], lung cancer [120], and neuronal differentiation [121]; Arginase 2 (ARG2), which has roles in suppressing macrophage cytotoxicity and myeloid-derived suppressor cell function [122] and is elevated in breast cancer [123]; Zinc-finger and BTB domain-containing protein 17 (ZBTB17/Miz1) which modulates Myc, a multifunctional nuclear phosphoprotein in cell cycle progression, apoptosis, and cellular transformation and which is enhanced in tumours [124]; Adenosine Deaminase, RNA Specific B1 (ADARB1), which is overexpressed in various cancer cell types and transformed stem cells [125]; Annexin A4 (ANXA4), the upregulation of which promotes the progression of tumour and chemoresistance of various cancers [126]; Major histocompatibility complex,
class II (HLA-DRB1), which besides known functions in autoimmunity, including the generation of anti-citrullination antibodies [127], is also associated to carcinoma [128].

Figure 1. STRING analysis (https://string-db.org/) showing putative binding partners (STRING combined score >0.4) of PAD2 and PAD4, identified and found to be present in exosomes and microvesicles EMVs based on a search by gene symbol in the Vesiclepedia protein data set. Lines between nodes represent the following: Green line = text mining; Blue line = from curated database; Pink line = experimentally determined.

6. PADs in Central Nervous System (CNS) Damage and Neuroprotective Effects of PAD Inhibitors

In two animal models of acute CNS damage, pharmacological pan-PAD inhibition has been shown to be neuroprotective in vivo following administration straight after insult and for up to two hours post-injury, indicating a clinically relevant time window for intervention [53,54,129]. Firstly, in a spinal cord injury model, significant reduction was observed in infarct size, accompanied by reduced neuronal cell death and histone H3 deimination, compared to non-treated control injuries [53]. Secondly, two murine models of neonatal hypoxic ischaemic encephalopathy (HIE), showed similar neuroprotective effects as estimated by volume infarct analysis, reduced cell death, and histone H3 deimination, and in
addition a significant impact on neuroinflammatory responses as reflected in reduced microglial activation in all affected brain regions [54]. The fact that these neuroprotective effects of PAD-inhibitors are translatable between CNS injury and animal models, is indeed promising for effective application also in other cases of neuronal damage. Interestingly, while increased protein deimination has been also detected in the pathology of traumatic brain injury [130], EMV release has been associated with cerebral hypoxia induced by acute ischaemic stroke [131,132] and mesenchymal stromal cell-derived EMVs have recently been shown to protect the foetal brain following hypoxia-ischaemia in an experimental ovine model [133], and to be neuroprotective in stroke [134,135] and traumatic brain injury [136] rat models. The significance of EMV release in relation to pharmacological PAD manipulation requires further investigation in acute CNS damage.

7. EMVs in Neurodegenerative Diseases

EMVs are increasingly being associated with neurodegenerative disease progression and pathologies [137–143]. In the CNS, EMVs have been shown to be produced by several cell types including neurones, microglia, oligodendrocytes, astrocytes, and embryonic neural stem cells [8,144–146] and to play important roles in the development and function of the nervous system [147]. Roles for EMVs in neurodegenerative disease progression include intercellular communication and neuroinflammation due to transport of parent-cell specific cargo that can be translated in recipient cells and also affect gene regulation [148–150]. In Amyotrophic Lateral Sclerosis (ALS), exosomes have for example been shown to export misfolded mutant superoxide dismutase 1 (SOD1) [151,152]; in relation to ALS and Frontotemporal dementia (FTD) to export TAR DNA-binding protein 43 (TDP-43) [153,154]; and there is increasing evidence emerging for critical roles for miRNA transport in the pathogenesis of FTD-ALS [155,156]. In tauopathies, EMVs have been shown to export phosphorylated tau [157,158]; in Parkinson’s disease (PD), exosomes were shown to export α-synuclein and leucine-rich repeat kinase 2 (LRRK2) [159–161]; and in Alzheimer’s disease (AD), they export amyloid β (Aβ) [162,163]. All of these proteins form aggregates involved in the disease pathologies [164]. As EMVs have the capability to travel further via the blood or cerebrospinal fluid, misfolded proteins may spread via this pathway in a prion-like manner [165–170]. In addition, functional effects of such a protein transport have been indicated for Aβ, which progressively accumulates in EMVs with age, while the β-site cleavage of amyloid precursor protein (APP) has been reported to occur inside EMVs [171]. Also, the phosphorylation of tau differs in exosomes compared to total cell lysates, indicating functional consequences for its seeding capability [157]. In AD, neuroinflammation has been linked to circulating TNFx [172–174], which causes nuclear translocation of PADs [94,95], and to neutrophil extracellular trap formation [175], which is PAD4-dependent [38,94] and causes externalization of deiminated histones [176] and release of active PAD enzymes [177]. In addition, α-synuclein induces TNF-α containing exosomes from microglia [161] while TNF-α has been shown to promote EMV shedding from endothelial cells [162]. In light of this increasing evidence for crucial roles of EMVs in neuroinflammation, and the transfer and spreading of neurodegenerative protein aggregates alongside other cargo, the mechanisms of EMV biogenesis and routes of modulation are pivotal. It has also to be considered that the primary changes in most neurodegenerative diseases occur in specific brain locations followed by propagation into well-defined brain regions. The levels of secretion and cargo composition may thus not be homogenous among brain regions [142].

8. PADS and Protein Deimination in Neurodegenerative Diseases

The evidence for critical roles of PADS in various neurodegenerative diseases is mounting [178–183]. A human RNA-Seq transcriptome and splicing database of glia, neurones, and vascular cells of the cerebral cortex shows highest levels of PAD2 in mature astrocytes, oligodendrocytes, and microglia [184]. In many cases where protein deimination has been associated with neurodegenerative diseases, including multiple sclerosis (MS) [185–188], AD, and PD, studies
have mainly focused on histological analysis of post mortem human samples. AD post mortem human brain samples display increased protein deimination [179–181,189–191] and deiminated proteins are present in amyloid-containing areas in amyloid-precursor-protein/presenilin1 (APP + PSEN1) transgenic AD mouse models [44,192].

Although some deiminated target proteins have been described, most remain to be identified. Using proteomic analysis of deiminated proteins in the injured CNS, several proteins with neurodegenerative implications were identified, including with roles in neuroinflammation and perivascular drainage of Aβ [53,54,193]. In AD patients, β-amyloid has been shown to be deiminated [44,181]. In hippocampal lysates from AD patients, glial fibrillary acidic protein (GFAP), an astrocyte-specific marker protein, and vimentin were identified as deiminated proteins and the deimination of GFAP was shown to be PAD2 specific [194]. In vitro studies demonstrated that amyloid peptides bind to PAD2, resulting in catalytic fibrillogenesis and formation of insoluble fibril aggregates [42]. In PD brain samples, increased levels of total protein deimination and deimination-positive extracellular plaques were observed [178]. Mutated misfolded α-synuclein protein has been related to increased protein deimination, amyotrophic lateral sclerosis (ALS) spinal cords show increase in deiminated proteins [44], and Creutzfeldt Jacob Disease (CJD) brain samples indicate roles for deiminated enolase [195]. In AD brains, pentatricopeptide repeat-containing protein 2 (PTCD2), a mitochondrial RNA maturation and respiratory chain function protein [196], is present in a deiminated form and is an antigen target of an AD diagnostic autoantibody. There are thus indications that disease-associated autoantibodies are generated due to the production and release of deiminated proteins and deiminated protein fragments, which may be released from damaged cells in regions of pathology [197,198]. In AD, both PAD2 and PAD4 were shown to be expressed in cerebral cortex and hippocampus, the brain regions most vulnerable to AD pathology, with PAD2 localized in activated astrocytes and PAD4 selectively expressed in neurones [197]. Evidence for increased PAD expression with progression of neurodegenerative disease has also been obtained by analysis of whole genome microarrays from mouse models carrying TAU and APP+PSEN1 mutations. Significant increase of PAD12 transcription was found in cortex and hippocampus in both mutants with disease progression compared to age matched controls [193]. PAD4 expression has been shown to co-localize with amyloid-β-42 in pyramidal neurones in cerebral cortex and in hippocampal large hilar neurones of the hippocampus, which were also surrounded by activated astrocytes and microglia. These neurones contained cytoplasmic accumulations of deiminated proteins [197]. Using iPSC neuronal models derived from fibroblasts from patients [199] carrying FTD/ALS associated valosin-protein containing mutations VCPR155C and VCPR191Q, both PAD2 and PAD4 expression, accompanied by significantly increased pan-protein deimination, has been observed compared to control (non-mutation carrying) neurones, with significant increases in histone H3 deimination in VCPR155C carrying neurones [193]. Similar changes were also observed for α-synuclein triplication [200] compared to control neurones [193]. The release of deiminated proteins from necrotic neurones has been thought to cause an increased exposure of deiminated neuronal proteins to the immune system. In addition, the continual return of cerebrospinal fluid to circulation via the arachnoid villi, containing modified deiminated proteins and protein fragments, has been suggested to be a key step in the ongoing pathology due to generation of autoantibodies [197]. PADs are thus expressed in neurones residing in brain regions that are engaged in neurodegenerative pathological changes and inflammatory changes such as reactive astrogliosis and microglial migration and invasion. This brain-region specific increase observed in PAD expression may affect local exosome or microvesicle release specifically, contributing to spread of pathology in these regions.

Figure 2 summarises the proposed interplay of PADs and EMVs in neurodegenerative disease pathologies.
Recent studies have emphasized roles for both EMVs and PAD enzymes in cancers and neurodegeneration. Critical roles for PADs and their pharmacological inhibition have been established in cancers and neuroinflammation. PAD-mediated mechanisms have been shown as a novel mediator in the biogenesis of EMVs, which may contribute in part to increasing EMV shedding from cancer cells and act as a protective mechanism to expel chemotherapeutic drugs. In the context of neurodegeneration, EMVs are increasingly implicated in the spread of pathologies via transfer of miRNAs and misfolded proteins. While Cl-amidine [201] remains the most used experimental pan-PAD inhibitor to date, the therapeutic potential and generation of second generation and selective isozyme-specific PAD inhibitors is receiving ever increasing attention [45,49,96,202–207]. The use of
targeted isozyme-selective PAD inhibitors in synergy with other EMV modulators—aimed at either exosomes, MVs, or both populations in conjunction—present promising combinatory therapies for both cancers and neurodegenerative diseases.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

AD Alzheimer’s disease
ALS Amyotrophic lateral sclerosis
APP Amyloid precursor protein
CJD Creutzfeldt Jacob Disease
CK Cytokeratin
Cl-Am Chlor-amidine
CNS Central nervous system
EV Extracellular vesicle
FTD Frontotemporal dementia
GFAP Gial fibrillary acidic protein
HDAC2 Histone deacetylase 2
HIE Hypoxic ischaemic encephalopathy
iPSC Induced pluripotent stem cell
LPS Lipopolysaccharide
MAC Membrane attack complex
MS Multiple sclerosis
MV Microvesicle
NET Neutrophil extracellular trap
PAD Peptidylarginine deiminase
PC3 Prostate cancer cell line
PD Parkinson disease
PNT2 Control benign prostate cell line
PSEN1 Presenilin 1
RA Rheumatoid arthritis
ROCK Rho/Rho-associated kinase
SNARE SNAP (Soluble NSF Attachment Protein) REceptor
SOD1 Superoxide dismutase 1
TDP-43 TAR DNA-binding protein 43
TNFx Tumour necrosis factor α
VCP Valosin containing protein

References

1. Ansa-Addo, E.A.; Lange, S.; Stratton, D.; Antwi-Baffour, S.; Cestari, I.; Ramirez, M.I.; McCrossan, M.V.; Inal, J.M. Human plasma membrane-derived vesicles halt proliferation and induce differentiation of THP-1 acute monocyctic leukemia cells. J. Immunol. 2010, 185, 5236–5246. [CrossRef] [PubMed]
2. Muralidharan-Chari, V.; Clancy, J.W.; Sedgwick, A.; D’Souza-Schorey, C. Microvesicles: Mediators of extracellular communication during cancer progression. J. Cell Sci. 2010, 12, 1603–1611. [CrossRef] [PubMed]
3. Turola, E.; Furlan, R.; Bianco, F.; Matteoli, M.; Verderio, C. Microglial microvesicle secretion and intercellular signaling. Front. Physiol. 2012, 3, 149. [CrossRef] [PubMed]
4. Kholia, S.; Ranghino, A.; Garnieri, P.; Lopatina, T.; Deregibus, M.C.; Rispoli, P.; Brizz, M.F.; Camussi, G. Extracellular vesicles as new players in angiogenesis. Vasc. Pharmacol. 2016, 86, 64–70. [CrossRef] [PubMed]
5. Piccin, A.; Murphy, W.G.; Smith, O.P. Circulating microparticles: Pathophysiology and clinical implications. Blood Rev. 2007, 21, 157–171. [CrossRef] [PubMed]
6. Inal, J.M.; Ansa-Addo, E.A.; Stratton, D.; Kholia, S.; Antwi-Baffour, S.S.; Jorfi, S.; Lange, S. Microvesicles in health and disease. Arch. Immunol. Ther. Exp. 2012, 60, 107–121. [CrossRef] [PubMed]
7. Tamai, K.; Kosgodage, U.; Azam, S.; Stratton, D.; Antwi-Baffour, S.; Lange, S. Blood/plasma secretome and microvesicles. *Biochim. Biophys. Acta* 2013, 1834, 2317–2325. [CrossRef] [PubMed]

8. Porro, C.; Trotta, T.; Panaro, M.A. Microvesicles in the brain: Biomarker, messenger or mediator? *J. Neuroimmunol* 2015, 288, 78–78. [CrossRef] [PubMed]

9. Giusti, I.; Dolo, V. Extracellular vesicles in prostate cancer: New future clinical strategies? *BioMed Res. Int.* 2014. [CrossRef]

10. Stratton, D.; Moore, C.; Antwi-Baffour, S.; Lange, S.; Inal, J. Microvesicles released constitutively from prostate cancer cells differ biochemically and functionally to stimulated microvesicles released through sublytic C5b-9. *Biochem. Biophys. Res. Commun.* 2015, 460, 589–595. [CrossRef] [PubMed]

11. Camussi, G.; Deregibus, M.C.; Bruno, S.; Grange, C.; Ronsato, V.; Tetta, C. Exosome/microvesicle-mediated epigenetic reprogramming of cells. *Am. J. Cancer Res.* 2011, 1, 98–110. [PubMed]

12. Théry, C.; Zitvogel, L.; Amigorena, S. Exosomes: Composition, biogenesis and function. *Nat. Rev. Immunol.* 2002, 2, 569–579. [PubMed]

13. Mackenzie, A.B.; Young, M.T.; Adinolfi, E.; Surprenant, A. Pseudoapoptosis induced by brief activation of ATP-gated P2X7 receptors. *J. Biol. Chem.* 2005, 280, 33968–33976. [CrossRef] [PubMed]

14. Coleman, M.L.; Sahai, E.A.; Yeo, M.; Boschi, M.; Dewar, A.; Olson, M.F. Membrane blebbing during apoptosis results from caspase-mediated activation of ROCK I. *Nat. Cell Biol.* 2001, 3, 339–345. [CrossRef] [PubMed]

15. Lynch, S.F.; Ludlam, C.A. Plasma microparticles and vascular disorders. *Br. J. Haematol.* 2007, 137, 36–48. [CrossRef] [PubMed]

16. Hanson, P.I.; Cashikar, A. Multivesicular body morphogenesis. *Annu. Rev. Cell Dev. Biol.* 2012, 28, 337–362. [CrossRef] [PubMed]

17. Hanson, P.I.; Cashikar, A. Multivesicular body morphogenesis. *Annu. Rev. Cell Dev. Biol.* 2012, 28, 337–362. [CrossRef] [PubMed]

18. Colombo, M.; Moita, C.; van Niel, G.; Kowal, J.; Vigneron, J.; Benaroch, P.; Manel, N.; Moita, L.F.; Théry, C.; Raposo, G. Analysis of ESCRT functions in exosome biogenesis, composition and secretion highlights the heterogeneity of extracellular vesicles. *J. Cell Sci.* 2013, 126, 5553–5565. [CrossRef] [PubMed]

19. Tamai, K.; Tanaka, N.; Nakano, T.; Kakazu, E.; Kondo, Y.; Inoue, J.; Shiina, M.; Fukushima, K.; Hoshino, T.; Sano, K.; et al. Exosome secretion of dendritic cells is regulated by Hrs, an ESCRT-0 protein. *Biochim. Biophys. Res. Commun.* 2010, 399, 384–390. [CrossRef] [PubMed]

20. Baietti, M.F.; Zhang, Z.; Mortier, E.; Melchior, A.; Degeest, G.; Geeraerts, A.; Depoortere, F.; Coomans, C.; Vermeiren, E.; et al. Syndecan-syntenin-ALIX regulates the biogenesis of exosomes. *Nat. Cell Biol.* 2012, 14, 677–685. [CrossRef] [PubMed]

21. Trajkovic, K.; Hsu, C.; Chiantia, S.; Rajendran, L.; Wenzel, D.; Wieland, F.; Schwille, P.; Brügger, B.; Simons, M. Ceramide triggers budding of exosome vesicles into multivesicular endosomes. *Science* 2008, 319, 1244–1247. [CrossRef] [PubMed]

22. Federici, C.; Petrucci, F.; Caimi, S.; Cesolini, A.; Logozzi, M.; Borghi, M.; D’Illo, S.; Lugini, L.; Violante, N.; Azzarito, T.; et al. Exosome release and low pH belong to a framework of resistance of human melanoma cells to cisplatin. *PLoS ONE* 2014, 9, e88193. [CrossRef] [PubMed]

23. Han, J.; Pluhackova, K.; Böckmann, R.A. The multifaceted role of SNARE proteins in membrane fusion. *Front. Physiol.* 2017, 8, 5. [CrossRef] [PubMed]

24. Fader, C.M.; Sánchez, D.G.; Mestre, M.B.; Colombo, M.I. TI-VAMP/VAMP7 and VAMP3/cellubrevin: Two v-SNARE proteins involved in specific steps of the autophagy/multivesicular body pathways. *Biochim. Biophys. Acta* 2009, 1793, 1901–1916. [CrossRef] [PubMed]

25. Góyorgy, B.; Szabó, T.G.; Pásztói, M.; Pál, Z.; Misjak, P.; Aradi, B.; László, V.; Pállinger, E.; Pap, E.; Kittel, A.; et al. Membrane vesicles, current state-of-the-art: Emerging role of extra-vesicular vesicles. *Cell Mol. Life Sci.* 2011, 68, 2667–2688. [CrossRef] [PubMed]

26. Kholia, S.; Jorfi, S.; Thompson, P.R.; Causey, C.P.; Nicholas, A.P.; Inal, J.M.; Lange, S. A novel role for peptidylarginine deiminases in microvesicle release reveals therapeutic potential of PAD inhibition in sensitizing prostate cancer cells to chemotherapy. *J. Extracell. Vesicles* 2015, 4, 26192. [CrossRef] [PubMed]

27. Jorfi, S.; Inal, J.M. The role of microvesicles in cancer progression and drug resistance. *Biochem. Soc. Trans.* 2013, 41, 293–298. [CrossRef] [PubMed]

28. Castellana, D.; Toti, F.; Freyssinet, J.M. Membrane microvesicles: Macromessengers in cancer disease and progression. *Thromb. Res.* 2010, 125, S84–S88. [CrossRef]
49. Wei, L.; Wasilewski, E.; Chakka, S.K.; Bello, A.M.; Moscarello, M.A.; Kotra, L.P. Novel inhibitors of protein arginine deiminase with potential activity in multiple sclerosis animal model. J. Med. Chem. 2013, 56, 1715–1722. [CrossRef] [PubMed]

50. Willis, V.C.; Gizinski, A.M.; Banda, N.K.; Causey, C.P.; Knuckley, B.; Cordova, K.N.; Luo, K.; Levitt, B.; Glogowska, M.; Chandra, P.; et al. α-N-benzoyl-N5-(2-chloro-1-iminoethyl)-l-ornithine amide, a protein arginine deiminase inhibitor, reduces the severity of murine collagen-induced arthritis. J. Immunol. 2011, 186, 4396–4404. [CrossRef] [PubMed]

51. Chumanevich, A.A.; Causey, C.P.; Knuckley, B.A.; Jones, J.E.; Poudyal, D.; Chumanevich, A.P.; Davis, T.; Matesic, L.E.; Thompson, P.R.; Hofseth, L.J. Suppression of colitis in mice by Cl-amidine: A novel peptidylarginine deiminase inhibitor. Am. J. Physiol. Gastrointest. Liver Physiol. 2011, 300, G929–G938. [CrossRef] [PubMed]

52. Smith, C.K.; Vivekanandan-Giri, A.; Tang, C.; Knight, J.S.; Mathew, A.; Padilla, R.L.; Gillespie, B.W.; Carmona-Rivera, C.; Liu, X.; Subramanian, V.; et al. Neutrophil extracellular trap-derived enzymes oxidize high-density lipoprotein: An additional proatherogenic mechanism in systemic lupus erythematosus. Arthritis Rheumatol. 2014, 66, 2532–2544. [CrossRef] [PubMed]

53. Lange, S.; Gögel, S.; Leung, K.Y.; Vernay, B.; Nicholas, A.P.; Causey, C.P.; Thompson, P.R.; Greene, N.D.; Ferretti, P. Protein deiminases: New players in the developmentally regulated loss of neural regenerative ability. Dev. Biol. 2011, 355, 205–214. [CrossRef] [PubMed]

54. Lange, S.; Rocha-Ferreira, E.; Thei, L.; Mawjee, P.; Bennett, K.; Thompson, P.R.; Subramanian, V.; Nicholas, A.P.; Peebles, D.; Hristova, M.; et al. Peptidylarginine deiminases: Novel drug targets for prevention of neuronal damage following hypoxic ischemic insult (HI) in neonates. J. Neurochem. 2014, 130, 555–562. [CrossRef] [PubMed]

55. Knight, J.S.; Luo, W.; O’Dell, A.A.; Yalavarthis, S.; Zhao, W.; Subramanian, V.; Guo, C.; Grenn, R.C.; Thompson, P.R.; Eitzman, D.T.; et al. Peptidylarginine deiminase inhibition reduces vascular damage and modulates innate immune responses in murine models of atherosclerosis. Circ. Res. 2014, 114, 947–956. [CrossRef] [PubMed]

56. Ginesa, A.; La, P.; Saladino, F.; Cassarà, D.; Nagase, H.; Vittorelli, M.L. The amount and proteolytic content of vesicles shed by human cancer cell lines correlates with their in vitro invasiveness. Anticancer Res. 1998, 18, 3433–3437. [PubMed]

57. Kim, H.K.; Song, K.S.; Park, Y.S.; Kang, Y.H.; Lee, Y.J.; Lee, K.R.; Kim, H.K.; Ryu, K.W.; Bae, J.M.; Kim, S. Elevated levels of circulating platelet microparticles, VEGF, IL-6 and RANTES in patients with gastric cancer: Possible role of a metastasis predictor. Eur. J. Cancer 2003, 39, 184–191. [CrossRef]

58. Zwicker, J.L.; Liebman, H.A.; Neuberg, D.; Lacroix, R.; Bauer, K.A.; Furie, B.C.; Furie, B. Tumor-derived tissue factor-bearing microparticles are associated with venous thromboembolic events in malignancy. Clin. Cancer Res. 2009, 15, 6830–6840. [CrossRef] [PubMed]

59. Jorfi, S.; Ansja-Addo, E.A.; Kholia, S.; Stratton, D.; Valley, S.; Lange, S.; Inal, J. Inhibition of microvesiculation sensitizes prostate cancer cells to chemotherapy and reduces docetaxel dose required to limit tumor growth in vivo. Sci. Rep. 2015, 5, 13006. [CrossRef] [PubMed]

60. Tang, K.; Zhang, Y.; Zhang, H.; Pingwei, X.; Jing, L.; Jingwei, M.; Meng, L.; Dapeng, L.; Kaitrai, F.; Guan-Xin, S.; et al. Delivery of chemotherapeutic drugs in tumour cell-derived microparticles. Nat. Commun. 2012, 3, 1282. [CrossRef] [PubMed]

61. Koch, R.; Aung, T.; Vogel, D.; Chapuy, B.; Wenzel, D.; Becker, S.; Sinzig, U.; Venkataramani, V.; von Mach, T.; Jacob, R.; et al. Nuclear trapping through inhibition of exosomal export by indomethacin increased cytostatic efficacy of doxorubicin and pixanthrone. Clin. Cancer Res. 2015, 22, 395–404. [CrossRef] [PubMed]

62. Muralidharan-Chari, V.; Kohan, H.G.; Asimakopoulos, A.G.; Sudha, T.; Sell, S.; Kannan, K.; Boroujerdi, M.; Davis, P.J.; Mousa, S.A. Microvesicle removal of anticancer drugs contributes to drug resistance in human pancreatic cancer cells. Oncotarget 2016, 7, 50365–50379. [CrossRef] [PubMed]

63. Saari, H.; Lazaro-Ibanez, E.; Viitala, T.; Vuorimaa-Laukkanen, E.; Siljander, P.; Yliperttula, M. Microvesicle-and exosome-mediated drug delivery enhances the cytotoxicity of paclitaxel in autologous prostate cancer cells. J. Control. Release 2016, 220, 727–737. [CrossRef] [PubMed]

64. Aubertin, K.; Silva, A.K.; Luciani, N.; Espinosa, A.; Djemat, A.; Charue, D.; Gallet, F.; Blanc-Brude, O.; Wilhelm, C. Massive release of extracellular vesicles from cancer cells after photodynamic treatment or chemotherapy. Sci. Rep. 2016, 18, 35376. [CrossRef] [PubMed]
65. Pascucci, L.; Coccè, V.; Bonomi, A.; Ami, D.; Ceccarelli, P.; Ciusani, E.; Viganò, L.; Locatelli, A.; Siston, F.; Doglia, S.M.; et al. Paclitaxel is incorporated by mesenchymal stem cells and released in exosomes that inhibit in vitro tumor growth: A new approach for drug delivery. *J. Control. Release* 2014, 192, 262–270. [CrossRef] [PubMed]

66. Soekmadji, C.; Nelson, C.C. The emerging role of extracellular vesicle-mediated drug resistance in cancers: Implications in advanced prostate cancer. *BioMed Res. Int.* 2015, 2015, 454837. [CrossRef] [PubMed]

67. Chang, X.; Han, J.; Pang, L.; Zhao, Y.; Yang, Y.; Shen, Z. Increased PADI4 expression in blood and tissues of patients with malignant tumors. *BMC Cancer* 2009, 9, 40. [CrossRef] [PubMed]

68. Xin, J.; Song, X. Role of peptidylarginine deiminase type 4 in gastric cancer. *Exp. Ther. Med.* 2016, 12, 3155–3160. [CrossRef] [PubMed]

69. Wang, L.; Chang, X.; Yuan, G.; Zhao, Y.; Wang, P. Expression of peptidylarginine deiminase type 4 in ovarian tumors. *Int. J. Biol. Sci.* 2010, 6, 454–464. [CrossRef] [PubMed]

70. Cherrington, B.D.; Zhang, X.; McElwee, J.L.; Morency, E.; Anguish, L.J.; Coonrod, S.A. Potential role for PADI2 in gene regulation in breast cancer cells. *PLoS ONE* 2012, 7, e41242. [CrossRef] [PubMed]

71. Guo, W.; Zheng, Y.; Xu, B.; Ma, F.; Li, C.; Zhang, X.; Wang, Y.; Chang, X. Investigating the expression, effect and tumorigenic pathway of PADI2 in tumors. *OncoTargets Ther.* 2017, 10, 1475–1485. [CrossRef] [PubMed]

72. Asaga, H.; Nakashima, K.; Senshu, T.; Ishigami, A.; Yamada, M. Immunocytochemical localization of peptidylarginine deiminase in human eosinophils and neutrophils. *J. Leukoc. Biol.* 2001, 70, 46–51. [PubMed]

73. Nakashima, K.; Hagiwara, T.; Yamada, M. Nuclear localization of peptidylarginine deiminase V and histone deimination in granulocytes. *J. Biol. Chem.* 2002, 277, 49562–49568. [CrossRef] [PubMed]

74. Li, P.; Yao, H.; Zhang, Z.; Li, M.; Luo, Y.; Thompson, P.R.; Gilmour, D.S.; Wang, Y. Regulation of p53 target gene expression by peptidylarginine deiminase 4. *Mol. Cell Biol.* 2008, 28, 4745–4758. [CrossRef] [PubMed]

75. Tanikawa, C.; Ueda, K.; Nakagawa, H.; Yoshida, N.; Nakamura, Y.; Matsuda, K. Regulation of protein citrullination through p53/PADI4 network in DNA damage response. *Cancer Res.* 2009, 69, 8761–8769. [CrossRef] [PubMed]

76. Zhang, X.; Gamble, M.J.; Stadler, S.; Cherrington, B.D.; Causey, C.P.; Thompson, P.R.; Roberson, M.S.; Kraus, W.L.; Coonrod, S.A. Genome-wide analysis reveals PADI4 cooperates with Elk-1 to activate c-Fos expression in breast cancer cells. *PLoS Genet.* 2011, 7, e1002112. [CrossRef] [PubMed]

77. Li, P.; Wang, D.; Yao, H.; Doret, P.; Hao, G.; Shen, Q.; Qiu, H.; Zhang, X.; Wang, Y.; Chen, G.; et al. Coordination of PADI4 and HDAC2 in the regulation of p53-target gene expression. *Oncogene* 2010, 29, 3153–3162. [CrossRef] [PubMed]

78. Yao, H.; Li, P.; Venter, B.J.; Zheng, S.; Thompson, P.R.; Pugh, B.F.; Wang, Y. Histone Arg modifications and p53 regulate the expression of OKL38, a mediator of apoptosis. *J. Biol. Chem.* 2008, 283, 20060–20068. [CrossRef] [PubMed]

79. Guo, Q.; Fast, W. Citrullination of inhibitor of growth 4 (ING4) by peptidylarginine deiminase 4 (PADI4) disrupts the interaction between ING4 and p53. *J. Biol. Chem.* 2011, 286, 17069–17078. [CrossRef] [PubMed]

80. Wang, Y.; Wysocka, J.; Sayegh, J.; Lee, Y.H.; Perlin, J.R.; Leonelli, L.; Sonnbuchner, L.S.; McDonald, C.H.; Cook, R.G.; Dou, Y.; et al. Human PAD4 regulates histone arginine methylation levels via demethylimination. *Science* 2004, 306, 279–283. [CrossRef] [PubMed]

81. Zheng, Y.; Zhao, G.; Xu, B.; Liu, C.; Li, C.; Zhang, X.; Chang, X. PADI4 has genetic susceptibility to gastric carcinoma and upregulates CXCR2, KRT14 and TNF-α expression levels. *Oncotarget* 2016, 7, 62159–62176. [CrossRef] [PubMed]

82. Kin Pong, U.; Subramanian, V.; Nicholas, A.P.; Thompson, P.R.; Ferretti, P. Modulation of calcium-induced cell death in human neural stem cells by the novel peptidylarginine deiminase-AIF pathway. *Biochim. Biophys. Acta* 2014, 1843, 1162–1171.

83. Cuthbert, G.L.; Daujat, S.; Snowden, A.W.; Erdjument-Bromage, H.; Hagiwara, T.; Yamada, M.; Schneider, R.; Gregory, P.D.; Tempst, P.; Bannister, A.J.; et al. Histone deimination antagonizes arginine methylation. *Cell* 2004, 118, 545–553. [CrossRef] [PubMed]

84. Zhang, X.; Bolt, M.; Guertin, M.J.; Chen, W.; Zhang, S.; Cherrington, B.D.; Slade, D.J.; Dreyton, C.J.; Subramanian, V.; Bicker, K.L.; et al. Peptidylarginine deiminase 2-catalyzed histone H3 arginine 26 citrullination facilitates estrogen receptor α target gene activation. *Proc. Natl. Acad. Sci. USA* 2012, 109, 13331–13336. [CrossRef] [PubMed]
85. Wang, H.; Xu, B.; Zhang, X.; Zheng, Y.; Zhao, Y.; Chang, X. PADI2 gene confers susceptibility to breast cancer and plays tumorigenic role via ACSD4, BIN3C And CA9 signaling. Cancer Cell. Int. 2016, 16, 61. [CrossRef] [PubMed]
86. Funayama, R.; Taniguchi, H.; Mizuma, M.; Fujishima, F.; Kobayashi, M.; Ohnuma, S.; Unno, M.; Nakayama, K. Protein-arginine deiminase 2 suppresses proliferation of colon cancer cells through protein citrullination. Cancer Sci. 2017, 108, 713–718. [CrossRef] [PubMed]
87. Cantarino, N.; Musulen, E.; Valero, V.; Peinado, M.A.; Peruco, M.; Moreno, V.; Forcales, S.V.; Douet, J.; Buschbeck, M. Downregulation of the deiminase PADI2 is an early event in colorectal carcinogenesis and indicates poor prognosis. Mol. Cancer Res. 2016, 14, 841–848. [CrossRef] [PubMed]
88. Stadler, S.C.; Vincent, C.T.; Fedorov, V.D.; Patsialou, A.; Cherrington, B.D.; Wakshlag, J.J.; Mohanan, S.; Zee, B.M.; Zhang, X.; Garcia, B.A.; et al. Dysregulation of PAD4-mediated citrullination of nuclear GSK3β activates TGF-β signaling and induces epithelial-to-mesenchymal transition in breast cancer cells. Proc. Natl. Acad. Sci. USA 2013, 110, 11851–11856. [CrossRef] [PubMed]
89. Cui, X.; Witalison, E.E.; Chumanevich, A.P.; Chumanevich, A.A.; Poudyal, D.; Subramanian, V.; Schetter, A.J.; Harris, C.C.; Thompson, P.R.; Hofseth, L.J. The induction of microRNA-16 in colon cancer cells by protein arginine deiminase inhibition causes a p53-dependent cell cycle arrest. PLoS ONE 2013, 8, e53791. [CrossRef] [PubMed]
90. Hurwitz, S.N.; Rider, M.A.; Bundy, J.L.; Liu, X.; Singh, R.K.; Meckes, D.G., Jr. Proteomic profiling of NCI-60 extracellular vesicles uncovers common protein cargo and cancer type-specific biomarkers. Oncotarget 2016, 7, 86999–87015. [CrossRef] [PubMed]
91. Hong, B.S.; Cho, J.H.; Kim, H.; Choi, E.J.; Rho, S.; Kim, J.; Kim, J.H.; Choi, D.S.; Kim, Y.K.; Hwang, D.; et al. Colorectal cancer cell-derived microvesicles are enriched in cell cycle-related mRNAs that promote proliferation of endothelial cells. BMC Genom. 2009, 10, 556. [CrossRef] [PubMed]
92. Chang, X.; Han, J. Expression of peptidylarginine deiminase type 4 (PAD4) in various tumors. Mol. Carcinog. 2006, 45, 183–196. [CrossRef] [PubMed]
93. Bawadekar, M.; Shim, D.; Johnson, C.J.; Warner, T.F.; Rebernick, R.; Damgaard, D.; Nielsen, C.H.; Pruijn, G.J.; Nett, J.E.; Shelef, M.A. Peptidylarginine deiminase 2 is required for tumour necrosis factor α-induced citrullination and arthritis, but not neutrophil extracellular trap formation. J. Autoimmun. 2017, 80, 39–47. [CrossRef] [PubMed]
94. Fuhrmann, J.; Thompson, P.R. Protein arginine methylation and citrullination in epigenetic regulation. ASC Chem. Biol. 2015, 11, 654–668. [CrossRef] [PubMed]
95. Mastronardi, F.G.; Wood, D.D.; Mei, J.; Rajmakers, R.; Tseveleki, V.; Dosch, H.M.; Probert, L.; Casaccia-Bonnefil, P.; Moscarello, M.A. Increased citrullination of histone H3 in multiple sclerosis brain and animal models of demyelination: A role for tumor necrosis factor-induced peptidylarginine deiminase 4 translocation. J. Neurosci. 2006, 26, 11387–11396. [CrossRef] [PubMed]
96. Asai, H.; Ikezu, S.; Tsunoda, S.; Medalla, M.; Luebbe, J.; Haydar, T.; Wolozin, B.; Butovsky, O.; Kügler, S.; Ikezu, T. Depletion of microglia and inhibition of exosome synthesis halt tau propagation. Nat. Neurosci. 2015, 18, 1584–1593. [CrossRef] [PubMed]
97. Combes, V.; Latham, S.L.; Wen, B.; Allison, A.C.; Grau, G.E. Diannexin down-modulates endothelial microparticle release by blocking membrane budding process. Int. J. Innov. Med. Health Sci. 2016, 7, 1–11. [CrossRef] [PubMed]
98. Dinkins, M.B.; Enasko, J.; Hernandez, C.; Wang, G.; Kong, J.; Helwa, I.; Liu, Y.; Terry, A.V., Jr.; Bieberich, E. Neutral sphingomyelinase-2 deficiency ameliorates Alzheimer’s disease pathology and improves cognition in the 5XFAD mouse. J. Neurosci. 2016, 36, 8653–8667. [CrossRef] [PubMed]
99. Kuzel, T.M.; Tallman, M.S.; Shevin, D.; Braud, E.; Kilton, I.; Johnson, P.; Kozlowski, J.; Vogelzang, N.J.; Blough, R.; Benson, A.B., 3rd. A phase II study of continuous infusion 5-fluorouracil in advanced hormone refractory prostate cancer. An Illinois Cancer Center Study. Cancer 1993, 72, 1965–1968. [CrossRef] [PubMed]
100. Darrah, E.; Rosen, A.; Giles, J.T.; Andrade, F. Peptidylarginine deiminase 2, 3 and 4 have distinct specificities against cellular substrates: Novel insights into autoantigen selection in rheumatoid arthritis. Ann. Rheum. Dis. 2012, 71, 92–98. [CrossRef] [PubMed]
101. Tarcza, E.; Marekov, L.N.; Mei, G.; Melino, G.; Lee, S.C.; Steinert, P.M. Protein unfolding by peptidylarginine deiminase. Substrate specificity and structural relationships of the natural substrates trichohyalin and filaggrin. J. Biol. Chem. 1996, 271, 30709–30716. [CrossRef] [PubMed]
102. Knuckle, B.; Causey, C.P.; Jones, J.E.; Bhatia, M.; Dreyton, C.J.; Osborne, T.C.; Takahara, H.; Thompson, P.R. Substrate specificity and kinetic studies of PADS 1, 3, and 4 identify potent and selective inhibitors of protein arginine deiminase 3. Biochemistry 2010, 49, 4852–4863. [CrossRef] [PubMed]

103. Assouh-Luty, C.; Raimakers, R.; Benckhuysen, W.E.; Stammen-Vogelzangs, J.; de Ru, A.; van Veenen, P.A.; Franken, K.L.; Drijfhout, J.W.; Pruin, G.J. The human peptidylarginine deiminases type 2 and type 4 have distinct substrate specificities. Biochim. Biophys. Acta 2014, 1844, 829–836. [CrossRef] [PubMed]

104. Arita, K.; Hashimoto, H.; Shimizu, T.; Nakashima, K.; Yamada, M.; Sato, M. Structural basis for Ca^{2+}-induced activation of human PAD4. Nat. Struct. Mol. Biol. 2004, 11, 777–783. [CrossRef] [PubMed]

105. Kan, R.; Jin, M.; Subramanian, V.; Causey, C.P.; Thompson, P.R.; Coon-Rod, S.A. Potential role for PADI-mediated histone citrullination in preimplantation development. BMC Dev. Biol. 2012, 12, 19. [CrossRef] [PubMed]

106. Bunnell, T.M.; Burbach, B.J.; Shimizu, Y.; Ervasti, J.M. β-Actin specifically controls cell growth, migration, and the G-actin pool. Mol. Biol. Cell 2011, 22, 4047–4058. [CrossRef] [PubMed]

107. Raposo, G.; Stoorvogel, W. Extracellular vesicles: Exosomes, microvesicles and friends. J. Cell Biol. 2013, 200, 373–383. [CrossRef] [PubMed]

108. van Beers, J.J.; Schwarte, C.M.; Stammen-Vogelzangs, J.; Oosterink, E.; Božič, B.; Pruijn, G.J. The rheumatoid arthritis synovial fluid citrullinome reveals novel citrullinated epitopes in apolipoprotein E, myeloid nuclear differentiation antigen, and β-actin. Arthritis Rheumatol. 2013, 65, 69–80. [CrossRef] [PubMed]

109. Soo, C.Y.; Song, Y.; Zheng, Y.; Campbell, E.C.; Riches, A.C.; Gunn-Moore, F.; Powis, S.J. Nanoparticle tracking analysis monitors microvesicle and exosome secretion from immune cells. Immunology 2012, 136, 192–197. [CrossRef] [PubMed]

110. Ercolani, L.; Florence, B.; Denaro, M.; Alexander, M. Isolation and complete sequence of a functional human glyceraldehyde-3-phosphate dehydrogenase gene. J. Biol. Chem. 1988, 263, 15335–15341. [PubMed]

111. Patterson, R.L.; van Rossum, D.B.; Kaplin, A.L.; Barrow, R.K.; Snyder, S.H. Inositol 1,4,5-trisphosphate receptor/GAPDH complex augments Ca^{2+} release via locally derived NADH. Proc. Natl. Acad. Sci. USA 2005, 102, 1357–1359. [CrossRef] [PubMed]

112. Xu, K.Y.; Becker, L.C. Ultrastructural localization of glycolytic enzymes on sarcoplasmic reticulum vesicles. J. Histochem. Cytochem. 1998, 46, 419–427. [CrossRef] [PubMed]

113. Butterfield, D.A.; Hardas, S.S.; Lange, M.L. Oxidatively modified glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and Alzheimer’s disease: Many pathways to neurodegeneration. J. Alzheimers Dis. 2010, 20, 369–393. [CrossRef] [PubMed]

114. Tisdale, E.J. Glyceraldehyde-3-phosphate dehydrogenase is required for vesicular transport in the early secretory pathway. J. Biol. Chem. 2001, 276, 2480–2486. [CrossRef] [PubMed]

115. McNee, G.; Eales, K.L.; Wei, W.; Williams, D.S.; Barkkuizen, A.; Bartlett, D.B.; Essex, S.; Anandram, S.; Filer, A.; Moss, P.A.; et al. Citrullination of histone H3 drives IL-6 production by bone marrow mesenchymal stem cells in MGUS and multiple myeloma. Leukemia 2017, 31, 373–381. [CrossRef] [PubMed]

116. Wang, Y.; Li, P.; Wang, S.; Hu, J.; Chen, X.A.; Wu, J.; Fisher, M.; Oshaben, K.; Zhao, N.; Gu, Y.; et al. Anticancer peptidylarginine deiminase (PAD) inhibitors regulate the autophagy flux and the mammalian target of rapamycin complex 1 activity. J. Biol. Chem. 2012, 287, 25941–25953. [CrossRef] [PubMed]

117. Kumari, N.; Dwarkakanath, B.S.; Das, A.; Bhatt, A.N. Role of interleukin-6 in cancer progression and therapeutic resistance. Tumour. Biol. 2016, 37, 11553–11572. [CrossRef] [PubMed]

118. Montanari, M.; Rossetti, S.; Cavalliere, C.; D’Aniello, C.; Malzone, M.G.; Vanacore, D.; di Franco, R.; La Mantia, E.; Iovane, G.; Piscitelli, R.; et al. Epithelial-mesenchymal transition in prostate cancer: An overview. Oncotarget 2017, 8, 35376–35389. [CrossRef] [PubMed]

119. Short, K.M.; Cox, T. Subclassification of the RBCC/TRIM superfamily reveals a novel motif necessary for microtubule binding. J. Biol. Chem. 2006, 281, 8970–8980. [CrossRef] [PubMed]

120. Zhan, W.; Han, T.; Zhang, C.; Xie, C.; Gan, M.; Deng, K.; Fu, M.; Wang, J.B. TRIM59 promotes the proliferation and migration of non-small cell lung cancer cells by upregulating cell cycle related proteins. PLoS ONE 2015, 10, e0142596. [CrossRef] [PubMed]

121. Yaguchi, H.; Okumura, F.; Takahashi, H.; Kano, T.; Kameda, H.; Uchigashima, M.; Tanaka, S.; Watanabe, M.; Sasaki, H.; Hatakeyama, S. TRIM67 protein negatively regulates Ras activity through degradation of 80K-H and induces neuritogenesis. J. Biol. Chem. 2012, 287, 12050–12059. [CrossRef] [PubMed]
122. El-Zaatari, M.; Kao, J.Y. Role of dietary metabolites in regulating the host immune response in Gastrointestinal disease. Front. Immunol. 2017, 8, 51. [CrossRef] [PubMed]

123. Singh, R.; Avliyakulov, N.K.; Braga, M.; Haykinson, M.J.; Martinez, L.; Singh, V.; Parveen, M.; Chaudhuri, G.; Pervin, S. Proteomic identification of mitochondrial targets of arginase in human breast cancer. PLoS ONE 2013, 8, e79242. [CrossRef]

124. Wolf, E.; Lin, C.Y.; Eilers, M.; Levens, D.L. Taming of the beast: Shaping Myc-dependent amplification. Trends Cell Biol. 2015, 25, 241–248. [CrossRef] [PubMed]

125. Flanagan, J.M.; Funes, J.M.; Henderson, S.; Wild, L.; Carey, N.; Boshoff, C. Genomics screen in transformed stem cells reveals RNASEH2A, PPAP2C, and ADAR1 as putative anticancer drug targets. Mol. Cancer Ther. 2009, 8, 249–260. [CrossRef] [PubMed]

126. Wei, B.; Guo, C.; Liu, S.; Sun, M.Z. Annexin A4 and cancer. Clin. Chim. Acta 2015, 447, 72–78. [CrossRef] [PubMed]

127. Chung, I.M.; Ketharnathan, S.; Thiruvengadam, M.; Rajakumar, G. Rheumatoid arthritis: The stride from research to clinical practice. Int. J. Mol. Sci. 2016, 17, 6. [CrossRef] [PubMed]

128. Liu, L.; Guo, W.; Zhang, J. Association of HLA-DRB1 gene polymorphisms with hepatocellular carcinoma risk: A meta-analysis. Minerva Med. 2017, 108, 176–184. [PubMed]

129. Lange, S. Peptidylarginine deiminases as drug targets in neonatal hypoxic-ischemic encephalopathy. Front. Neurol. 2016, 7, 22. [CrossRef] [PubMed]

130. Lazarus, R.C.; Buonora, J.E.; Flora, M.N.; Freedy, J.G.; Holstein, G.R.; Martinelli, G.P.; Jacobowitz, D.M.; Mueller, G.P. Protein citrullination: A proposed mechanism for pathology in traumatic brain injury. Front. Neurol. 2015, 6, 204. [CrossRef] [PubMed]

131. Cherian, P.; Hankey, G.J.; Eikelboom, J.W.; Thom, J.; Baker, R.I.; McQuillan, A.; Staton, J.; Yi, Q. Endothelial and platelet activation in acute ischemic stroke and its etiological subtypes. Stroke 2003, 34, 2132–2137. [CrossRef] [PubMed]

132. Simak, J.; Gelderman, M.P.; Yu, H.; Wright, V.; Baird, A.E. Circulating endothelial microparticles in acute ischemic stroke: A link to severity, lesion volume and outcome. J. Thromb. Haemost. 2006, 6, 1296–1302. [CrossRef] [PubMed]

133. Ophelders, D.R.; Wolfs, T.G.; Jellema, R.K.; Zwanenburg, A.; Andriessen, P.; Delhaas, T.; Ludwig, A.K.; Radtke, S.; Peters, V.; Janssen, L.; et al. Mesenchymal stromal cell-derived extracellular vesicles protect the fetal brain after hypoxia-ischemia. Stem. Cells Transl. Med. 2016, 5, 754–763. [CrossRef] [PubMed]

134. Xin, H.; Li, Y.; Cui, Y. Systemic administration of exosomes released from mesenchymal stromal cells promote functional recovery and neurovascular plasticity after stroke in rats. J. Cereb. Blood Flow. Metab. 2013, 33, 1711–1715. [CrossRef] [PubMed]

135. Döppner, T.R.; Herz, J.; Görgens, A. Extracellular vesicles improve post-stroke neuroregeneration and prevent post-ischemic immunosuppression. Stem. Cells Transl. Med. 2015, 4, 1131–1143. [CrossRef] [PubMed]

136. Zhang, Y.; Chopp, M.; Meng, Y. Effect of exosomes derived from multipluripotent mesenchymal stromal cells on functional recovery and neurovascular plasticity in rats after traumatic brain injury. J. Neurosurg. 2015, 122, 856–867. [CrossRef] [PubMed]

137. Tomlinson, P.R.; Zheng, Y.; Fischer, R.; Heidasch, R.; Gardiner, C.; Evetts, S.; Hu, M.; Wade-Martins, R.; Turner, M.R.; Morris, J.; et al. Identification of distinct circulating exosomes in Parkinson’s disease. Ann. Clin. Transl. Neurol. 2015, 2, 353–361. [CrossRef] [PubMed]

138. Agosta, F.; Dalla Libera, D.; Spinelli, E.G.; Finardi, A.; Canu, E.; Bergami, A.; Bocchio Chiavetto, L.; Baronio, M.; Comi, G.; Martino, G.; et al. Myeloid microvesicles in cerebrospinal fluid are associated with myelin damage and neuronal loss in mild cognitive impairment and Alzheimer disease. Ann. Neurol. 2014, 76, 813–825. [CrossRef] [PubMed]

139. Joshi, P.; Turola, E.; Ruiz, A.; Bergami, A.; Libera, D.D.; Benussi, L.; Giussani, P.; Magnani, G.; Comi, G.; Legname, G.; et al. Microglia convert aggregated amyloid-β into neurotoxic forms through the shedding of microvesicles. Cell Death Differ. 2014, 21, 582–593. [CrossRef] [PubMed]

140. Liu, S.; Hossinger, A.; Göbbels, S.; Vorberg, I.M. Prions on the run: How extracellular vesicles serve as delivery vehicles for self-templating protein aggregates. Prion 2017, 11, 98–112. [CrossRef] [PubMed]

141. Thompson, A.G.; Gray, E.; Heman-Ackah, S.M.; Mäger, I.; Talbot, K.; Andaloussi, S.E.; Wood, M.J.; Turner, M.R. Extracellular vesicles in neurodegenerative disease—Pathogenesis to biomarkers. Nat. Rev. Neurol. 2016, 12, 346–357. [CrossRef] [PubMed]
142. Levy, E. Exosomes in the diseased brain: First insights from in vivo studies. Front. Neurosci. 2017, 11, 142. [CrossRef] [PubMed]
143. Soria, F.N.; Pampliega, O.; Bourdenx, M.; Meissner, W.G.; Bezard, E.; Dehay, B. Exosomes, an unmasked culprit in neurodegenerative diseases. Front. Neurosci. 2017, 11, 26. [CrossRef] [PubMed]
144. Schiera, G.; Proia, P.; Alberti, C.; Mineo, M.; Savettieri, G.; di Liegro, I. Neurons produce FGF2 and VEGF and secrete them at least in part by shedding extracellular vesicles. J. Cell Mol. Med. 2007, 11, 1384–1394. [CrossRef] [PubMed]
145. Falchi, A.M.; Sogos, V.; Saba, F.; Piras, M.; Congiu, T.; Piludu, M. Astrocytes shed large membrane vesicles that contain mitochondria, lipid droplets and ATP. Histochem. Cell Biol. 2013, 139, 221–231. [CrossRef] [PubMed]
146. Bianco, F.; Pravettoni, E.; Colombo, A.; Schenk, U.; Möller, T.; Matteoli, M.; Verderio, C. Astrocyte-derived ATP induces vesicle shedding and IL-1β release from microglia. J. Immunol. 2005, 174, 7268–7277. [CrossRef] [PubMed]
147. Frühbeis, C.; Fröhlich, D.; Kuo, W.P.; Amphornrat, J.; Thilemann, S.; Saab, A.S.; Kirchhoff, F.; Möbius, W.; Goebbels, S.; Nave, K.A.; et al. Neurotransmitter-triggered transfer of exosomes mediates oligodendrocyte-neuron communication. PloS Biol. 2013, 11, e1001604. [CrossRef] [PubMed]
148. Valadi, H.; Ekstrom, K.; Bossios, A.; Sjostrand, M.; Lee, J.J.; Lotvall, J.O. Exosomemediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat. Cell Biol. 2007, 9, 654–659. [CrossRef] [PubMed]
149. Pegtel, D.M.; Peferoen, L.; Amor, S. Extracellular vesicles as modulators of cell-to-cell communication in the healthy and diseased brain. Philos. Trans. R. Soc. Lond. B Biol. Sci. 2014, 369, 1652. [CrossRef] [PubMed]
150. Coleman, B.M.; Hill, A.F. Extracellular vesicles—Their role in the packaging and spread of misfolded proteins associated with neurodegenerative diseases. Semin. Cell Dev. Biol. 2015, 40, 89–96. [CrossRef] [PubMed]
151. Basso, M.; Pozzi, S.; Tortarolo, M.; Fiordaliso, F.; Bisighini, C.; Pasetto, L.; Spaltro, G.; Lidonnici, D.; Gensano, F.; Battaglia, E.; et al. Mutant copper-zinc superoxide dismutase (SOD1) induces protein secretion pathway alterations and exosome release in astrocytes: Implications for disease spreading and motor neuron pathology in amyotrophic lateral sclerosis. J. Biol. Chem. 2013, 288, 15699–15711. [CrossRef] [PubMed]
152. Grad, L.I.; Yerbury, J.J.; Turner, B.J.; Guest, W.C.; Pokrishevsky, E.; O’Neill, M.A.; Yanai, A.; Silverman, J.M.; Zeineddine, R.; Corcoran, L.; et al. Intercellular propagated misfolding of wild-type Cu/Zn superoxide dismutase occurs via exosome-dependent and -independent mechanisms. Proc. Natl. Acad. Sci. USA 2014, 111, 3620–3625. [CrossRef] [PubMed]
153. Nonaka, T.; Masuda-Suzukake, M.; Arai, T.; Hasegawa, Y.; Akatsu, H.; Obi, T.; Yoshida, M.; Murayama, S.; Mann, D.M.; Akiyama, H.; et al. Prion-like properties of pathological TDP-43 aggregates from diseased brains. Cell Rep. 2013, 4, 124–134. [CrossRef] [PubMed]
154. Feneberg, E.; Steinacker, P.; Lehner, S.; Schneider, A.; Walther, P.; Thal, D.R.; Linsenmeier, M.; Ludolph, A.C.; Otto, M. Limited role of free TDP-43 as a diagnostic tool in neurodegenerative diseases. Amyotroph. Lateral Scler. Front. Degener. 2014, 15, 351–356. [CrossRef] [PubMed]
155. Eitan, C.; Hornstein, E. Vulnerability of microRNA biogenesis in FTD-ALS. Brain Res. 2016, 15, 105–111. [CrossRef] [PubMed]
156. Gascon, E.; Gao, F.B. The emerging roles of microRNAs in the pathogenesis of frontotemporal dementia-amyotrophic lateral sclerosis (FTD-ALS) spectrum disorders. J. Neurogenet. 2014, 28, 30–40. [CrossRef] [PubMed]
157. Saman, S.; Kim, W.; Raya, M.; Visnick, Y.; Miro, S.; Saman, S.; Jackson, B.; McKee, A.C.; Alvarez, V.E.; Lee, N.C.; et al. Exosome-associated tau is secreted in tauopathy models and is selectively phosphorylated in cerebrospinal fluid in early Alzheimer disease. J. Biol. Chem. 2012, 287, 3842–3849. [CrossRef] [PubMed]
158. Bellingham, S.A.; Guo, B.; Hill, A.F. The secret life of extracellular vesicles in metal homeostasis and neurodegeneration. Biol. Cell 2015, 107, 389–418. [CrossRef] [PubMed]
159. Danzer, K.M.; Kranich, L.R.; Ruf, W.P.; Cagsal-Getkin, O.; Winslow, A.R.; Zhu, L.; Vanderburg, C.R.; McLean, P.J. Exosomal cell-to-cell transmission of α synuclein oligomers. Mol. Neurodegener. 2012, 7, 42. [CrossRef] [PubMed]
160. Fraser, K.B.; Moehle, M.S.; Daher, J.P.; Webber, P.J.; Williams, J.Y.; Stewart, C.A.; Yacoubian, T.A.; Cowell, R.M.; Dokland, T.; Ye, T.; et al. LRRK2 secretion in exosomes is regulated by 14-3-3. Hum. Mol. Genet. 2013, 22, 4988–5000. [CrossRef] [PubMed]
161. Chang, C.; Lang, H.; Gen, N.; Wang, J.; Li, N.; Wang, X. Exosomes of BV-2 cells induced by α-synuclein: Important mediator of neurodegeneration in PD. Neurosci. Lett. 2013, 548, 190–195. [CrossRef] [PubMed]

162. Eyre, J.; Burton, J.O.; Saleem, M.A.; Mathieson, P.W.; Topham, P.S.; Brunskil, N.J. Monocyte- and endothelial-derived microparticles induce an inflammatory phenotype in human podocytes. Nephron. Exp. Nephrol. 2011, 119, 58–66.

163. Eitan, E.; Hutchison, E.R.; Marosi, K.; Comotto, J.; Mustapić, M.; Nigam, S.M.; Suire, C.; Maharana, C.; Jicha, G.A.; Liu, D.; et al. Extracellular vesicle-associated Aβ mediates trans-neuronal bioenergetic and Ca2+-handling deficits in Alzheimer’s disease models. NPJ Aging Mech. Dis. 2016, 2, 16019. [CrossRef] [PubMed]

164. Jucker, M.; Walker, L.C. Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. Nature 2013, 501, 45–51. [CrossRef] [PubMed]

165. Polanco, J.C.; Scicluna, B.J.; Hill, A.F.; Götz, J. Extracellular vesicles isolated from brains of rTg4510 mice seed tau aggregation in a threshold-dependent manner. J. Biol. Chem. 2016, 291, 12445–12466. [CrossRef] [PubMed]

166. Fevrier, B.; Vilette, D.; Archer, F.; Loew, D.; Vidal, M.; Laude, H.; Raposo, G. Cells release prions in association with exosomes. Proc. Natl. Acad. Sci. USA 2004, 101, 9683–9688. [CrossRef] [PubMed]

167. Leblanc, P.; Alais, S.; Porto-Carreiro, I.; Lehmann, S.; Grassi, J.; Raposo, G.; Darlix, J.L. Retrovirus infection strongly enhances scrapie infectivity release in cell culture. EMBO J. 2006, 25, 2674–2685. [CrossRef] [PubMed]

168. Vella, L.J.; Sharples, R.A.; Lawson, V.A.; Masters, C.L.; Cappai, R.; Hill, A.F. Packaging of prions into exosomes is associated with a novel pathway of PrP processing. J. Pathol. 2007, 211, 582–590. [CrossRef] [PubMed]

169. Alais, S.; Simoes, S.; Baas, D.; Lehmann, S.; Raposo, G.; Darlix, J.L.; Leblanc, P. Mouse neuroblastoma cells release prion infectivity associated with exosomal vesicles. Biol. Cell 2008, 100, 603–615. [CrossRef] [PubMed]

170. Mattei, V.; Baronec, M.G.; Tasciotti, V.; Garofalo, T.; Longo, A.; Boller, K.; Lower, J.; Misasi, R.; Montrasio, F.; Sorice, M. Paracrine diffusion of PrP(C) and propagation of prion infectivity by plasma membrane-derived microvesicles. PLoS ONE 2009, 4, e5057. [CrossRef] [PubMed]

171. Hosseinzadeh, S.; Zahmatkesh, M.; Zarrindast, M.R.; Hassanzadeh, G.R.; Karimian, M.; Sarrafnejad, A. Elevated CSF and plasma microparticles in a rat model of streptozotocin-induced cognitive impairment. Behav. Brain Res. 2013, 256, 503–511. [CrossRef] [PubMed]

172. Fillit, H.; Ding, W.H.; Buee, L.; Kalman, J.; Altstiel, L.; Lawlor, B.; Wolf-Klein, G. Elevated circulating tumor necrosis factor levels in Alzheimer’s disease. Nat. Med. 1991, 1999, 318–320. [CrossRef]

173. Prokop, S.; Miller, K.R.; Heppner, F.L. Microglia actions in Alzheimer’s disease. Acta Neuropathol. 2013, 126, 461–477. [CrossRef] [PubMed]

174. Heppner, F.L.; Ransohoff, R.M.; Becher, B. Immune attack: The role of inflammation in Alzheimer disease. Nat. Rev. Neurosci. 2015, 16, 358–372. [CrossRef] [PubMed]

175. Zenaro, E.; Pietroniro, E.; Bianca, V.D.; Piacentino, G.; Marongiu, L.; Budui, S.; Turano, E.; Rossi, B.; Angiari, S.; Dusi, S.; et al. Neutrophils promote Alzheimer’s disease-like pathology and cognitive decline via LFA-1 integrin. Nat. Med. 2015, 21, 880–886. [CrossRef] [PubMed]

176. Brinkmann, V.; Zychlinsky, A. Neutrophil extracellular traps: Is immunity the second function of chromatin? J. Cell Biol. 2012, 198, 773–783. [CrossRef] [PubMed]

177. Rohrbach, A.S.; Arandjelovic, S.; Mowen, K.A. Physiological Pathways of PAD Activation and Citrullinated Epitope Generation. In Protein Deimination in Human Health and Disease; Bhattacharya, S., Nicholas, A., Eds.; Springer: New York, NY, USA, 2014; Chapter 1; ISBN: 978-1-4614-8316-8.

178. Nicholas, A.P., Bhattacharya, S.K., Eds.; Springer Science and Business Media: New York, NY, USA, 2014; Chapter 13.
181. Nicholas, A.P. Dual immunofluorescence study of citrullinated proteins in Alzheimer diseased frontal cortex. *Neurosci. Lett.* **2013**, *545*, 107–111. [CrossRef] [PubMed]

182. Jang, B.; Jin, J.K.; Jeon, Y.C.; Cho, H.J.; Ishigami, A.; Choi, K.C.; Carp, R.I.; Maruyama, N.; Kim, Y.S.; Choi, E.K. Involvement of peptidylarginine deiminase-mediated post-translational citrullination in pathogenesis of sporadic Creutzfeldt-Jakob disease. *Acta Neuropathol.* **2009**, *119*, 199–210. [CrossRef] [PubMed]

183. Yang, L.; Tan, D.; Piao, H. Myelin basic protein citrullination in multiple sclerosis: A potential therapeutic target for the pathology. *Neurochem. Res.* **2016**, *41*, 1845–1856. [CrossRef] [PubMed]

184. Zhang, Y.; Chen, K.; Sloan, S.A.; Bennett, M.L.; Scholze, A.R.; O’Keeffe, S.; Phatnani, H.P.; Guarnieri, P.; Caneda, C.; Ruderisch, N.; et al. An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. *J. Neurosci.* **2014**, *34*, 11929–11947. [CrossRef] [PubMed]

185. Moscarello, M.A.; Wood, D.D.; Ackerley, C.; Boulias, C. Myelin in multiple sclerosis is developmentally immature. *J. Clin. Investig.* **1994**, *94*, 146–154. [CrossRef] [PubMed]

186. Musse, A.A.; Li, Z.; Ackerley, C.A.; Bienzle, D.; Lei, H.; Poma, R.; Moscarello, M.A.; Mastronardi, F.G. Peptidylarginine deiminase 2 (PAD2) overexpression in transgenic mice leads to myelin loss in the central nervous system. *Dis. Model Mech.* **2008**, *1*, 229–240. [CrossRef] [PubMed]

187. Wood, D.D.; Ackerley, C.A.; Brand, B.; Zhang, L.; Rajmakers, R.; Mastronardi, F.G.; Moscarello, M.A. Myelin localization of peptidylarginine deiminases 2 and 4: Comparison of PAD2 and PAD4 activities. *Lab. Investig.* **2008**, *88*, 354–364. [CrossRef] [PubMed]

188. Bradford, C.M.; Ramos, I.; Cross, A.K.; Haddock, G.; McQuaid, S.; Nicholas, A.P.; Woodroofe, M.N. Localisation of citrullinated proteins in normal appearing white matter and lesions in the central nervous system in multiple sclerosis. *J. Neuroimmunol.* **2014**, *273*, 85–95. [CrossRef] [PubMed]

189. Nicholas, A.P.; King, J.L.; Sambandam, T.; Echols, J.D.; Gupta, K.B.; McNinnis, C.; Whitaker, J.N. Immunohistochemical localization of citrullinated proteins in adult rat brain. *J. Comp. Neurol.* **2003**, *459*, 251–266. [CrossRef] [PubMed]

190. Nicholas, A.P.; Sambandam, T.; Echols, J.D.; Tourtellotte, W.W. Increased citrullinated glial fibrillary acidic protein in secondary progressive multiple sclerosis. *J. Comp. Neurol.* **2004**, *473*, 128–136. [CrossRef] [PubMed]

191. Nicholas, A.P.; Sambandam, T.; Echols, J.D.; Barnum, S.R. Expression of citrullinated proteins in murine experimental autoimmune encephalomyelitis. *J. Comp. Neurol.* **2005**, *486*, 254–266. [CrossRef] [PubMed]

192. Borchelt, D.R.; Thinakaran, G.; Eckman, C.B.; Lee, M.K.; Davenport, F.; Ratovitsky, T.; Prada, C.M.; Kim, G.; Seekins, S.; Yager, D.; et al. Familial Alzheimer’s disease-linked presenilin 1 variants elevate Aβ1–42/1–40 ratio in vitro and in vivo. *Neuron* **1996**, *17*, 1005–1013. [CrossRef]

193. Lange, S.; Wray, S.; Devine, M.; Matarin, M.; Hardy, J. Protein Deimination in Protein Misfolding Disorders—Modelled in Human Induced Pluripotent Stem Cells (iPSCs). In *Protein Deimination in Human Health and Disease*; Nicholas, A.P., Bhattacharya, S.K., Eds.; Springer Science and Business Media: New York, NY, USA, 2017; Volume 2, Chapter 24.

194. Ishigami, A.; Matsumoto, H.; Handa, S.; Nakamura, M.; Nakaya, S.; Uchida, Y.; Saito, Y.; Murayama, S.; Jang, B.; Jeon, Y.C.; et al. Mass spectrometric identification of citrullination sites and immunohistochemical detection of citrullinated glial fibrillary acidic protein in Alzheimer’s disease brains. *J. Neurosci. Res.* **2015**, *93*, 1664–1674. [CrossRef] [PubMed]

195. Jang, B.; Jeon, Y.C.; Choi, J.K.; Park, M.; Kim, J.I.; Ishigami, A.; Maruyama, N.; Carp, R.I.; Kim, Y.S.; Choi, E.K. Peptidylarginine deiminase modulates the physiological roles of enolase via citrullination: Links between altered multifunction of enolase and neurodegenerative diseases. *Biochem. J.* **2012**, *445*, 183–192. [CrossRef] [PubMed]

196. Lightowlers, R.N.; Chrzanowska-Lightowlers, Z.M. Human pentatricopeptide proteins: Only a few and what do they do? *RNA Biol.* **2013**, *10*, 1433–1438. [CrossRef] [PubMed]

197. Acharya, N.K.; Nagele, E.P.; Han, M.; Coretti, N.J.; DeMarshall, C.; Kosciuk, M.C.; Boulos, P.A.; Nagele, R.G. Neuronal PAD4 expression and protein citrullination: Possible role in production of autoantibodies associated with neurodegenerative disease. *J. Autoimmun.* **2012**, *38*, 369–380. [CrossRef] [PubMed]

198. Nagele, E.; Han, M.; Demarshall, C.; Belinka, B.; Nagele, R. Diagnosis of Alzheimer’s disease based on disease-specific autoantibody profiles in human sera. *PLoS ONE* **2011**, *6*, e23112. [CrossRef] [PubMed]
199. Wray, S.; Self, M.; NINDS Parkinson’s Disease iPSC Consortium; NINDS Huntington’s Disease iPSC Consortium; NINDS ALS iPSC Consortium; Lewis, P.A.; Taanman, J.W.; Ryan, N.S.; Mahoney, C.J.; Liang, Y.; et al. Creation of an open-access, mutation-defined fibroblast resource for neurological disease research. *PLoS ONE* 2012, 7, e43099.

200. Devine, M.J.; Ryten, M.; Vodicka, P.; Thomson, A.J.; Burdon, T.; Houlden, H.; Cavalieri, F.; Nagano, M.; Drummond, N.J.; Taanman, J.W.; et al. Parkinson’s disease induced pluripotent stem cells with triplication of the α-synuclein locus. *Nat. Commun.* 2011, 2, 440. [CrossRef] [PubMed]

201. Luo, Y.; Knuckley, B.; Lee, Y.H.; Stallcup, M.R.; Thompson, P.R. A fluoroacetamidine-based inactivator of protein arginine deiminase 4: Design, synthesis, and in vitro and in vivo evaluation. *J. Am. Chem. Soc.* 2006, 128, 1092–1093. [CrossRef] [PubMed]

202. Bozdag, M.; Dreker, T.; Henry, C.; Tosco, P.; Vallaro, M.; Fruttero, R.; Scozzafava, A.; Carta, F.; Supuran, C.T. Novel small molecule protein arginine deiminase 4 (PAD4) inhibitors. *Bioorg. Med. Chem. Lett.* 2013, 23, 715–719. [CrossRef] [PubMed]

203. Ferretti, P.; U, K.P.; Vagaska, B.; Merchant, R.; Matthews, C.J.; Marson, C.M. Discovery of a structurally novel, drug-like and potent inhibitor of peptidylarginine deiminase. *Med. Chem. Commun.* 2013, 4, 1109–1113. [CrossRef]

204. Subramanian, V.; Knight, J.S.; Parelkar, S.; Anguish, L.; Coonrod, S.A.; Kaplan, M.J.; Thompson, P.R. Design, synthesis, and biological evaluation of tetrazole analogs of Cl-amidine as protein arginine deiminase inhibitors. *J. Med. Chem.* 2015, 58, 1337–1344. [CrossRef] [PubMed]

205. Trabocchi, A.; Pala, N.; Krimmelbein, I.; Menchi, G.; Guarna, A.; Sechi, M.; Dreker, T.; Scozzafava, A.; Supuran, C.T.; Carta, F. Peptidomimetics as protein arginine deiminase 4 (PAD4) inhibitors. *J. Enzym. Inhib. Med. Chem.* 2015, 30, 466–471. [CrossRef] [PubMed]

206. Jamali, H.; Khan, H.A.; Tjin, C.C.; Ellman, J.A. Cellular activity of new small molecule protein arginine deiminase 3 (PAD3) inhibitors. *ACS Med. Chem. Lett.* 2016, 7, 847–851. [CrossRef] [PubMed]

207. Muth, A.; Subramanian, V.; Beaumont, E.; Nagar, M.; Kerry, P.; McEwan, P.; Srinath, H.; Clancy, K.; Parelkar, S.; Thompson, P.R. Development of a selective inhibitor of protein arginine deiminase 2. *J. Med. Chem.* 2017, 60, 3198–3211. [CrossRef] [PubMed]

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