Research Article

Progranulin (Pgrn) Facilitates Anti-Inflammation And Pulpitis Repair in Vivo And in Vitro Through Tnfr2/14-3-3ε Signalling Complex – A Systematic Review

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Abstract

Background: Progranulin (PGRN) is a key regulator of inflammation, controlling tissue damage and various pathophysiological processes. Involved in biological functions from embryonic development to adult tissue maintenance and repair, PGRN presents many opportunities for further study. Tumor necrosis factor α (TNFα) signals through TNF receptors 1 (TNFR1) and 2 (TNFR2). TNFR1 is widely expressed and primarily initiates pro-inflammatory pathways via soluble TNF (sTNF). TNFR2 expression is sparse, mostly on regulatory T cells (Tregs), and its binding to membrane-bound TNF (mTNF) often starts immune regulation and tissue regeneration. Dental pulp is a vascular, innervated mesenchymal connective tissue encased in mineralized dentin. Its primary components are fibroblastic cells and a layer of odontoblasts that produce dentin. The pulp-dentin complex acts as a single unit, providing protective systems against environmental stimuli. Inflammation is the initial response to irritants, with tertiary dentin deposition occurring in response to injury, which can be reactionary or reparative depending on the extent of the disturbance.

Material and Methods: Major databases such as Medline were explored detailed literature search in resulting in a systematic review pertaining to progranulin (PGRN) facilitates anti-inflammation and pulpitis repair in vivo and in vitro through TNFR2/14-3-3ε signalling complex.

Results: Eight original research scientific articles dated between 2020 – 2024 pertaining to mentioned topic were highlighted.

Conclusions: Progranulin (PGRN) influences numerous processes in health and disease. Its immune-regulating and growth factor qualities prevent excessive tissue damage while promoting tissue recovery. This makes PGRN a critical focus for studies in inflammatory diseases and regenerative medicine. Specifically, PGRN stimulates pulp tissue growth, osteogenic differentiation, and mineralization in both healthy and inflamed conditions. Detailed information regarding the is discussed progranulin (PGRN) facilitates anti-inflammation and pulpitis repair in vivo and in vitro through TNFR2/14-3-3ε signalling complex in this systematic review.

Key word: TNF-α; TNFRs; progranulin, Autoimmunity; Inflammation; TNF receptors. Cell cycle, pleiotropic growth factor, tumor, human dental pulp stem cells.

INTRODUCTION:

A multipurpose growth factor-like protein called progranulin (PGRN) has been shown to be an important regulator of tissue healing and inflammatory responses, including the complex environment of the tooth pulp. The knowledge of PGRN's anti-inflammatory and reparative functions has greatly increased in recent years, even though it was first identified for its growth-promoting qualities in a variety of cell types as well as its role in cancer and neurodegeneration. Its ability to regulate the powerful signaling pathways involving tumor necrosis factor (TNF) and its receptors (TNFR1 and TNFR2) is a crucial component of its activity. For diseases like pulpitis, an infection of the tooth pulp tissue, where controlling inflammation is essential for effective pulp preservation and regeneration, this relationship is especially pertinent. Pro-inflammatory cytokines, particularly TNF-alpha (TNF-α), are frequently involved in the inflammatory cascade in pulpitis and, if untreated, can cause tissue damage. By directly binding to TNF receptors, especially TNFR2, and blocking TNF-alpha binding and downstream signaling, PGRN functions as an endogenous antagonist to TNF-alpha signaling. This process aids in preventing tissue damage and reducing excessive inflammation. The function of PGRN in relation to pulpitis and repair dentinogenesis is particularly highlighted by recent studies. Recombinant human PGRN (rhPGRN) treatment dramatically reduces inflammatory markers and increases the expression of anti-inflammatory mediators like interleukin 10 (IL-10), according to research using rat models of pulpitis and human dental pulp stem cells (hDPSCs). The pro-inflammatory NF-κB/p65 pathway is inhibited because of the activation of the TNFR2 signaling pathway, which in turn involves the 14-3-3 ε protein. Additionally, PGRN actively promotes the healing process while simultaneously reducing the inflammatory response. As demonstrated by elevated alkaline phosphatase (ALP) activity, mineralized nodule

formation, and dentin sialophosphoprotein (DSPP) expression, it promotes the growth and differentiation of hDPSCs into dentin-forming cells (odontoblasts). PGRN's promise as a novel therapeutic agent for crucial pulp therapy is highlighted by its dual action of anti-inflammation and healing, which is mainly mediated via the TNFR2 pathway. This approach offers a promising method for protecting and repairing damaged dental pulp tissue.

MATERIAL AND METHODS:

"progranulin" AND "inflammation" AND "TNFR2'' were the words used in MEDLINE database using advance search strategy targeting different article categories between 2020 to 2024. The result was 68 articles, out of which we selected 8 articles based in the inclusion criteria. Inclusion criteria was of case studies and scientific literature between 2020-2024. Exclusion criteria was of scientific literature irrelevant to the specific search. This systematic review was conducted to determine importance of progranulin (PGRN) facilitates anti-inflammation and pulpitis repair in vivo and in vitro through TNFR2/14-3-3ε signalling complex following the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). PubMed, Lilacs, Embase, Scopus, and Web of Science were the source of electronic databases. The search strategy used Boolean operators (AND and OR): [ALL ("progranulin") AND (inflammation OR TNF OR TNFR2 OR dental pulp OR immunity) AND (growth factor)]. The following data were collected: first author, year, country of study, type of study and outcome. The quality of studies was assessed using the STROBE (Strengthening the Reporting of Observational Studies) checklist.

RESULTS:

Eight articles were included in this systematic review based on the selection criteria. We analyzed and mentioned in the eight articles reviewed. This included only relevant research articles and excluded articles pertaining to nonspecific search terms.

Table 1 – An overview

Author	Title	Journal	Outcome
Jing Chen, Miao Yu, Xiao Li, Qin-Feng Sun, Cheng-Zhe Yang, Pi-Shan Yang	Progranulin promotes osteogenic differentiation of human periodontal ligament stem cells via tumor necrosis factor receptors to inhibit TNF-α sensitized NF-kB and activate ERK/JNK signaling	Chen J, Yu M, Li X, Sun QF, Yang CZ, Yang PS. Progranulin promotes osteogenic differentiation of human periodontal ligament stem cells via tumor necrosis factor receptors to inhibit TNF-α sensitized NF-kB and activate ERK/JNK signaling. Journal of Periodontal Research. 2020 Jun;55(3):363-73.doi: 10.1111/jre.12720.	Progranulin promotes osteogenic differentiation via TNFR1
Miao Yu, Long Sun, Pengfei Ba, Linxia Li, Jing Chen, Qinfeng Sun	Progranulin promotes osteogenic differentiation of periodontal membrane stem cells in both inflammatory and non-inflammatory conditions	Yu M, Sun L, Ba P, Li L, Chen J, Sun Q. Progranulin promotes osteogenic differentiation of periodontal membrane stem cells in both inflammatory and non-inflammatory conditions. Journal of International Medical Research. 2021 Aug;49(8):03000605211032508.doi : 10.1177/03000605211032508	PGRN promotes PDL proliferation, osteogenic differentiation, and mineralization in both inflammatory and non-inflammatory conditions
Sha Leng, Linyi Liu, Weizhe Xu, Fan Yang, Jing Du, Ling Ye, Dingming Huang, Lan Zhang	Inflammation down regulates stromal cell-derived factor 1α in the early phase of pulpitis	Leng S, Liu L, Xu W, Yang F, Du J, Ye L, Huang D, Zhang L. Inflammation down regulates stromal cell-derived factor 1α in the early phase of pulpitis. Cytokine. 2022 Oct 1;158:155983.doi: 10.1016/j.cyto.2022.155983.	In early phase of pulpitis, inflammation suppressed SDF-1α by up-regulating TNFR2
Qian Chen, ZuPing Wu, Liang Xie	Progranulin is essential for bone homeostasis	Chen Q, Wu Z, Xie L. Progranulin is essential for bone homeostasis and	PGRN help in bone formation, as well as in

	and immunology	immunology. Annals of the New York Academy of Sciences. 2022 Dec;1518(1):58-68. doi: 10.1111/nyas.14905	physiological and TNF-α-mediated inflammatory conditions
Richard O Williams, Felix Il Clanchy, Yi-Shu Huang, Wen-Yi Tseng, Trevor W Stone	TNFR2 signalling in inflammatory diseases	Williams RO, Clanchy FI, Huang YS, Tseng WY, Stone TW. TNFR2 signalling in inflammatory diseases. Best Practice & Research Clinical Rheumatology. 2024 May 1;38(2):101941. doi:10.1016/j.berh.2024. 101941	pro-inflammatory effects of TNF are mediated by TNFR1, whereas TNFR2 is mainly involved in immune homeostasis and tissue healing
Wenchuan Liu, Aimei Song, Yixi Wu, Pizhang Gong, Jingjing Zhao, Liguo Zhang, Xinyang Liu, Ruwei Wang, Hongmei Guo, Pishan Yang	Enhanced immunomodulation and periodontal regeneration efficacy of subgingivally delivered progranulin-loaded hydrogel as an adjunct to non-surgical treatment for Class II furcation involvement in dogs	Liu W, Song A, Wu Y, Gong P, Zhao J, Zhang L, Liu X, Wang R, Guo H, Yang P. Enhanced immunomodulation and periodontal regeneration efficacy of subgingivally delivered progranulin-loaded hydrogel as an adjunct to non-surgical treatment for Class II furcation involvement in dogs. Journal of Clinical Periodontology. 2024 Jun;51(6):774-86. doi: 10.1111/jcpe.13955.	Subgingival delivery of the PGRN/GelMA complex could be a promising non-surgical adjunctive therapy for anti-inflammation, immunomodulation, and periodontal regeneration.
Liguo Zhang, Fujiao Nie, Jingjing Zhao, Shutong Li, Wenchuan Liu, Hongmei Guo, Pishan Yang	PGRN is involved in macrophage M2 polarization regulation through TNFR2 in periodontitis	Zhang L, Nie F, Zhao J, Li S, Liu W, Guo H, Yang P. PGRN is involved in macrophage M2 polarization regulation through TNFR2 in periodontitis. Journal of Translational Medicine. 2024 Apr 30;22(1):407. doi: 10.1186/s12967-024-05214-7	PGRN promotes macrophage M2 polarization through binding to TNFR2 in both pro- and anti-inflammatory microenvironments
Abdulelah Alrshedan, Mona Elsafadi, Manikandan Muthurangan, Solaiman Al-Hadlaq	Tumor Necrosis Factor Superfamily 14 Regulates the Inflammatory Response of Human Dental Pulp Stem Cells	Alrshedan A, Elsafadi M, Muthurangan M, Al-Hadlaq S. Tumor Necrosis Factor Superfamily 14 Regulates the Inflammatory Response of Human Dental Pulp Stem Cells. Current Issues in Molecular Biology. 2024 Dec 11;46(12):13979. doi.org/10.3390/cimb46120836	TNFSF14 could effectively reduce the inflammatory reaction by decreasing the levels of pro-inflammatory cytokines

DISCUSSION

Inflammation of the dentin-pulp complex results in cellular and molecular events that aim to remove the infection and promote wound healing.[1] Several cell types have the potential to detect any pathogen within the pulp–dentin complex, including odontoblasts, which are the first line of defence.[2] These cells express pattern-recognition receptors (PRRs), particularly Toll-like receptors (TLRs), which can recognize pathogen-associated molecular patterns (PAMPs).[3] Nuclear factor-kappa B (NF-κB) and p38 mitogen-activated protein (MAP) kinase pathways have been recognized as controls for a wide range of inflammatory mediators.[4] Thus, activation of NF-κB and MAP kinase in these cells is essential for regulating inflammation and tissue repair mechanisms.[5]

Pulp inflammation, or pulpitis, triggers a complex local immune response involving the cytokine tumor necrosis factor α (TNFα), which signals via two receptors: TNFR1 and TNFR2.[6] Progranulin (PGRN) plays a crucial, protective role in this process by acting as an endogenous antagonist that directly binds to both TNFRs, with a higher affinity for TNFR2.[7] PGRN limits excessive tissue damage and promotes a regenerative environment in the dental pulp by promoting pulp cell proliferation, osteogenic differentiation, and the formation of reparative dentin, primarily through a TNFR2-dependent pathway.[8] The balance

between PGRN and TNFα signaling is therefore a critical determinant of whether pulp inflammation resolves towards healing or progresses to irreversible damage.[9]

Tumor necrosis factor α (TNFα) is an essential signaling protein in the innate and adaptive immune systems. It also plays an important role in tissue degeneration and repair.[10] It is now recognized that the expression of TNF receptor 2 (TNFR2) is more limited than that of TNF receptor 1 (TNFR1).[11] The soluble TNF-mediated signaling pathway *via* TNFR1 drives a predominantly pro-inflammatory program whereas membrane bounded TNF binding to TNFR2 primarily initiates immune modulation and tissue regeneration.[12] TNF α plays a vital role in many physiological and pathological conditions. It is essential for the regulation of embryonic development, the sleep–wake cycle, lymph node follicle, and germinal centre formation, also play role in inflammation and immunity.[13] They mediate both acute and chronic systematic inflammatory reactions under conditions of infection or autoimmunity, it also causes cell apoptosis and necrosis under specific conditions.[14]

Tumor necrosis factor α exerts its function *via* two different type I transmembrane receptors, TNFR1 and TNFR2. Each has a characteristic extracellular domain, a transmembrane segment, and intracellular domain.[15] TNFR1 is ubiquitously expressed on nearly all cells in the body and can be activated by both mTNFα and sTNFα.[16] TNFR2, conversely, is restricted to thymic T lymphocytes, endothelial cells, microglia, and oligodendrocytes, and can only be fully initiated by mTNFα.[17] Other salient features of TNFR2 are that cellular activation status highly regulates its expression and unlike TNFR1, it does not contain a cytoplasmic death domain.[18]

It is well accepted that TNFα binding to TNFR1 activates two different intricate signal pathways: the maintenance of cell survival and the promotion of inflammatory cytokine expression; cell apoptosis and necrosis.[19] When TNFα binds to TNFR1, this interacts with TNFR type 1-associated death domain protein (TRADD), which recruits receptor interacting protein-1 (RIP-1) and TNF receptor-associated factor-2 (TRAF-2) to form Signal complex I.[20] Signal complex I can trigger NF-κB, which launches the transcriptions of many different genes including those associated with cell survival, production of inflammatory cytokines, and antiapoptotic gene pathways.[21] Recently, several studies have demonstrated that TNFR2 promotes a remarkable degree of cell activation, migration, and proliferation. TNF receptor 2 provides a critical contribution to neural survival and regeneration.[22] In the mouse model, TNFR2 showed a protective function by activating the Akt signaling pathway, these findings provide that TNF/TNFR2 serves as principal players in oligodendrocyte regeneration.[23] Several studies indicated that TNFR2 agonists are active in pancreatic regeneration, cardioprotection, remyelination, and in stem cell proliferation.[24]

Progranulin is alternatively identified in the literature as granulin-epithelin precursor, proepithelin, prostate cancer cell derived growth factor or acrogranin.[25] In humans, the gene is situated on chromosome 17q21.32, whereas the mouse gene is located on chromosome 11.[26] The proteolysis of progranulin by, elastase releases the granulin modules as peptides, the granulins. These are biologically active, although generally less potent than the intact progranulin protein.[27] PGRN is highly expressed in epithelial cells, certain types of neurons, and macrophages and skeletal muscle, chondrocytes, adipose tissue, hematopoietic cells, and immune cells, including T cells and DCs.[28] It has multiple physiological functions and is involved in many types of disease processes, including autoimmune disorders, cancer, and neurodegenerative diseases.[29]

PGRN, as a growth factor, promotes cell proliferation and is crucial to the development and generation of fast-growing epithelial, endothelial, and cancer cells.[30] PGRN levels are elevated in many types of cancer, including breast cancer, ovarian cancer, and cholangiocarcinoma.[31] Macrophage-derived PGRN is a key regulatory factor in the processes of inflammation and wound healing.[32] Its expression is increased in activated microglia in many neurodegenerative diseases, including Creutzfeldt-Jakob disease, motor neuron disease, multiple sclerosis, and Alzheimer's disease.[33]

PGRN also expressed in adipose tissues and is a key adipokine, mediating high-fat-induced insulin resistance, hence regulating the main pathological mechanisms of diabetes and obesity.[34] It has also been found to be highly expressed in a subpopulation of neutrophils that can promote antibody diversity in B cells.[35] PGRN also binds with TLR9 and assists in the recruitment of CpG oligodeoxynucleotides in macrophages, a process that is critical for the elimination of infection.[36]

PGRN-TNFR INTERACTIONS - PGRN was first found to bind to TNFR in a yeast two-hybrid system when screening for PGRN-binding proteins by using PGRN as bait.[37] Direct interaction between PGRN and TNFR showed that PGRN selectively binds to both TNFR1 and TNFR2, and that it binds to TNFR2 with much higher affinity than TNF-α.[38] PGRN showed therapeutic effects in various TNF-mediated inflammatory arthritis models, including collagen-induced arthritis and spontaneous arthritis.[39] Authors further generated an engineered molecule called Atsttrin that only contained half Grn F, A, C, and was found to still bind to TNFR. Atsttrin was shown to have even better therapeutic effects than PGRN in treating inflammatory arthritis.[40] PGRN blocked TNF-α-induced inflammatory osteoclastogenesis and protected BMP-2-mediated ectopic bone formation in TNF-α transgenic mice.[41] PGRN-derived Atsttrin was also reported to stimulate bone regeneration through inhibiting TNF signaling. It was incorporated into 3D-printed hydroxyapatite scaffolds, and used to stimulate bone regeneration.[42]

TNFR 2 is the binding receptor of growth factor PGRN. The TNDR 2 explains the specific mechanism of PGRN's anti-TNFα-induced inflammatory response.[43] PGRN directly binds TNFR 1 and TNFR 2, especially TNFR 2, and inhibits the function of TNF-α. Based on the analysis of PGRN/TNFR 2 binding fragments, PGRN-derived engineering proteins were constructed.[44] Recombinant protein Atsttrin selectively binds TNFR 2 to inhibit TNF-TNFRS binding and TNF-α induced inflammatory response.[45] PGRN and RANK inhibit osteoclast differentiation and osteoporosis in mice, thus providing a new candidate protein for osteoporosis drug

development.[46] PGRN plays an anti-inflammatory role in various inflammatory diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Alzheimer's disease, atherosclerosis, septicemia, and bacterial pneumonia by interfering with TNF receptor signaling.[47] PGRN is related to its effect on regulatory T (Treg) cells. It can inhibit inflammation and treat inflammatory arthritis.[48]

PGRN-mediated amplification and activation of Treg cells and the production of IL-10 depend on JNK signals but not on known ERK and PI3K pathways.[49] PGRN can stimulate various intracellular pathways to promote cell proliferation, migration, and transformation, also, an important regulator of glucose metabolism and insulin sensitivity.[50] PGRN also generates inflammatory factors through the Wnt/β- catenin signaling pathway and actively mediates autophagy. Moreover, PGRN has a substantial negative correlation with the expression of beta-catenin in psoriatic skin.[51] In the context of dental pulp inflammation (pulpitis), the molecular interplay between progranulin (PGRN), tumor necrosis factor receptors (TNFR), and 14-3-3 proteins is emerging as a critical regulatory mechanism.[52] A key aspect of this protective pathway involves 14-3-3 proteins, which function as essential scaffolding molecules that modulate their binding partners' activities and localization.[53] The 14-3-3ε isoform interacts with components of the TNFR2 complex, such as NF-κB/p65, to significantly inhibit the inflammatory cascade and promote regenerative processes like dentinogenesis.[54]

The 14–3-3 protein was first identified in bovine brain homogenate by Moore in 1967, 14–3-3 is a family of highly homologous proteins encoded by different genes and comprised different isoforms.[55] 14–3-3 is abundant in the brain and has also been detected in almost all tissues. Although 14–3-3 is mainly a cytoplasm protein, it is also found in the plasma membrane, nucleus, Golgi apparatus, chloroplasts, and mitochondria.[56] More than 1,200 binding partners of 14–3-3 have been identified, further demonstrating the important regulatory role of 14–3-3 in various processes, such as signaling, cell cycle regulation, neural development, and stress response.[57] 14–3-3ε, a member of the 14–3-3 protein family, is encoded by the *YWHAE* gene. In humans, *YWHAE* is located on the 17th chromosome and involved in cell adhesion, cell cycle regulation, signal transduction, and other biological processes.[58] It is closely associated with the development of numerous diseases, including cardiovascular and neurodegenerative diseases. Interestingly, 14–3-3ε is associated with aggressive migration and poor prognosis in various cancers.[59]

TNFα is a pro-inflammatory cytokine that plays diverse roles in the development of inflammatory diseases, viral infections, and cardiovascular diseases.[60] TNFα activates the NF-κB and mitogen-activated protein kinase (MAPK) pathways, which play a crucial role in the expression of pro-inflammatory cytokines and apoptosis and necrosis.[61] The TNFR2/14–3-3ε complex promotes an anti-inflammatory phenotype in macrophages affected by inflammatory arthritis, thereby being a potentially novel target for the clinical management of rheumatoid arthritis and osteoarthritis.[62] Studies also demonstrated that 14–3-3ε binds directly to CD13 to trigger an inflammatory response, inducing a catabolic phenotype like that observed in osteoarthritis.[63] PGRN in anti-infection, innate immunity, and immune regulation, it is necessary to present its intricate involvement in the inflammatory response with its recruitment into sites of inflammation and competition between inflammatory mediators.[64] PGRN acts by increasing the accumulation of neutrophils, macrophages, blood vessels, and fibroblasts in acute skin injury, but in acute infection, PGRN inhibits LPS-mediated IL-6, TNF-α, and MCP-1 cytokine release from macrophages.[65]

Chronic inflammation, is often caused by uncontrolled immune reactions, dysregulated, proinflammatory cytokine production, and the persistence of pathogens.[66] There are two membrane receptors of TNF-α: TNFR1 and TNFR2. TNFR1 is widely expressed in most cell lines and primary tissues, although TNFR2 is preferentially expressed on cells of the hematopoietic lineage.[67] TNF-α activates the caspase pathway and NF-κB pathway to induce apoptosis and expression of proinflammatory cytokines through TNFR1 and activates the AP-1 and NF-κB pathway to promote proliferation through TNFR2.[68] PGRN was discovered as a novel ligand of TNFR1 and TNFR2 receptors. PGRN blocks TNF-α-mediated signaling pathways by competing with TNF-α binding to TNFR1/2.[69] Another example of the inverse relationship of PGRN and TNF-α levels involves studies concerning the development of bone demineralization, mainly, osteopenia.[70]

It has been found that osteopenic phenotypes expressed significantly lower levels of PGRN, as well as of IL-13 and IL-10, and notably higher levels of TNF-α, IL-17, and IL-6.[71] Increasing PGRN levels resulted in an augmentation of concentrations of IL-13, IL-10, and 25-(OH) vitamin D, as well as a decrease in TNF-α and IL-17 concentration.[72] Therefore, the action of PGRN also plays a significant role in osteocytic metabolism via mechanisms involving TNFR signaling.[73] Therefore, it can be speculated that the balance between PGRN and TNF-α is very critical to the initiation and progression of both chronic autoimmune disorders. [74]

In the intricate landscape of inflammatory regulation, the molecular triad of progranulin (PGRN), tumor necrosis factor receptors (TNFRs), and 14-3-3 proteins play a pivotal role in maintaining tissue homeostasis and promoting regeneration, particularly within susceptible tissues like dental pulp.[75] PGRN serves as an endogenous guardian, directly engaging TNFRs to counteract the potent pro-inflammatory signals typically initiated by TNFα binding to TNFR1.[76] This antagonism shifts the balance towards a reparative response, heavily favoring the TNFR2-mediated pathway, which is associated with immune regulation and tissue healing.[77] The crucial link in this protective cascade is the family of 14-3-3 proteins, which act as dynamic scaffolders and signaling modulators.[78] Specific isoforms, such as 14-3-3ε, are integral to the TNFR2 signaling complex. They interact with key downstream signaling molecules, like NF-κB/p65, to effectively suppress pro-inflammatory gene expression.[79] To conclusion, the sophisticated interplay between PGRN, TNFRs, and 14-3-3 proteins represent a vital regulatory network against inflammation.[80]

CONCLUSION

Progranulin (PGRN) is a complex protein with diverse functional properties relevant to inflammatory diseases and regenerative medicine. Its normal function in the central nervous system (CNS) remains largely unknown, despite understanding some of its peripheral activity. The link between PGRN mutations and neurodegeneration highlights the need for research into both intracellular and secreted PGRN roles in neuronal maintenance and survival, as well as its function in microglial activity and CNS inflammation, focusing on expression regulation and molecular consequences. PGRN is also overexpressed in several cancer types, contributing to progression and offering potential strategies for improved diagnosis and treatment. Separately, studies indicate TNFR modulates inflammatory responses in human dental pulp stem cells, reducing pro-inflammatory cytokines while increasing anti-inflammatory ones, suggesting therapeutic potential in inflammation management.

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