Progranulin Binding Proteins

Subjects: Biochemistry & Molecular Biology

Contributor: Elisa Ventura, Giacomo Ducci, Reyes Benot Dominguez, Valentina Ruggiero, Antonino Belfiore, Elena Sacco, Marco Vanoni, Renato V. Iozzo, Antonio Giordano, Andrea Morrione

Progranulin is a pleiotropic growth factor with important physiological roles in embryogenesis and maintenance of adult tissue homeostasis. Progranulin pleiotropic action depends on its modular structure and its ability to interact with a broad range of molecules, including extracellular soluble proteins, components of the extracellular matrix, membrane proteins and proteins of the endoplasmic reticulum (ER)/Golgi/lysosome network.

Keywords: progranulin ; solid tumors ; RTKs

1. Introduction

Progranulin is a pluripotent growth factor with important roles in several physiological processes. Progranulin is expressed in both the embryo and placenta, where it modulates embryo growth [1] and implantation [2], as well as placenta formation [3]. In adult tissues, progranulin regulates tissue regeneration [4][5], promotes angiogenesis [6], modulates the immune response [7][8] and is implicated in host defense against bacterial infections [8][9]. In addition, progranulin is a key neurotrophic factor as, in fact, it promotes neuronal survival and neurite growth [10][11], modulates neuroinflammation [12] and regulates lysosome function in neurons [13][14]. On the other hand, progranulin dysregulation is involved in several diseases [15] and therefore has attracted attention as a potential therapeutic target [16]. Progranulin mutations and heterozygous or homozygous loss are associated with various and severe pathologies affecting the brain, including frontotemporal dementia and lysosomal storage diseases [17][18][19]. Dysregulated progranulin is also implicated in autoimmune diseases [20]. Progranulin is overexpressed in several cancer types, including hematological malignancies, where it exerts a critical role in tumor progression.

2. Progranulin Binding Proteins

Progranulin pleiotropic action depends on its modular structure and its ability to interact with a broad range of molecules, including extracellular soluble proteins, components of the extracellular matrix, membrane proteins and proteins of the endoplasmic reticulum (ER)/Golgi/lysosome network. The list of proteins interacting with progranulin is continuously growing. Recently, new progranulin-binding proteins have been identified using the ligand receptor capture technique in the neuron-like cell line NCS-34, but the biological relevance of these novel interactions is still unknown [21]. Progranulin-binding proteins can be divided into three main categories: (1) extracellular proteins; (2) membrane proteins; and (3) ER/Golgi/lysosome network proteins. In addition, it has been reported that progranulin and some granulin repeats can localize to the nucleus, where they interact with the Tat/positive transcription elongation factor b (P-TEFb) and inhibit Tat transactivation [22][23].

2.1. Progranulin Interaction with Extracellular Proteins

Secreted progranulin not only interacts with various extracellular proteases, which are responsible for progranulin processing into granulins, as well as with proteins protecting progranulin from proteolytic degradation, but also with different components of the extracellular matrix (ECM), including perlecan [24][25], cartilage oligomeric matrix protein (COMP) [26] and extracellular matrix protein 1 [27]. The interaction of progranulin with perlecan is mediated by granulin modules F and B and the first two-laminin- and epidermal growth factor-like repeats of progranulin and perlecan, respectively [24], and modulates tumor angiogenesis [24]. Progranulin interaction with COMP, mediated by the granulin module A, potentiates progranulin-dependent stimulation of chondrocyte proliferation [26], while the association of progranulin with extracellular matrix protein 1 negatively regulates chondrogenesis and endochondral ossification [27].

2.2. Progranulin Interaction with Membrane Proteins and Membrane Receptors

Progranulin can bind several membrane proteins and cell membrane receptors, such as sortilin [13], prosaposin [28], tumor-necrosis factor receptor (TNFR) 1 and 2 [7], DR3 [29], four Notch receptors [30], DLK1 [31], EphA2 [32], RET [21] and Toll-like receptor (TLR)9 [9], and these interactions are highly context-dependent.

Sortilin and prosaposin are principally responsible for progranulin lysosomal trafficking. Sortilin belongs to the vacuolar protein sorting 10 (Vps10) family of receptors and its binding to progranulin leads to progranulin endocytosis and trafficking into lysosomes [13]. Secreted progranulin can interact with soluble prosaposin, in turn mediating progranulin internalization and lysosomal sorting by interacting with the mannose-6-phosphate receptor (MRP6) or the low-density lipoprotein receptor-related protein 1 (LRP1) [28]. Both sortilin and prosaposin can mediate progranulin delivery into lysosomes from either the extracellular space or the secretory pathway [13][33]. Evidence suggests that the interactions of progranulin with sortilin and/or prosaposin are particularly relevant in neurological cells [34]. Whether the interaction of progranulin with other membrane receptors, including RTKs, leads to progranulin internalization is not well established.

Progranulin binds to TNFR1 and TNFR2 on immune cells, mostly macrophages and Tregs, competing with TNF-alpha for receptor binding, thereby inhibiting TNF-alpha pro-inflammatory activity [7]. It is important to mention to that progranulin interaction with TNFRs remains controversial, since other groups failed to confirm a direct binding of progranulin to TNFRs [35][36][37]. These discrepancies might be due to technical differences in the surface plasmon resonance (SPR) experimental approaches used by different groups [38]. In addition, progranulin binds to the TNFR1 homolog death receptor 3 (DR3), thereby inhibiting DR3 binding to its natural ligand TNF-like ligand 1 (TL1A) [29].

Progranulin binds to Notch receptors by interacting with the extracellular domain of the receptor, as demonstrated for the interaction with Notch1 [30]. Progranulin activates Notch signaling pathways, promoting peripheral nerve regeneration and motor function recovery [30]. In addition, progranulin interacts with DLK1, a modulator of the Notch signaling pathway, but the biological relevance of this interaction is unknown [31].

In bladder cancer cells, progranulin binds to and activates ephrinA1-independent EphA2 non-canonical signaling [32] favoring tumor progression, while in the neuron-like cell line NSC-34, progranulin binds to RET and promotes its tyrosine-phosphorylation [21].

Finally, progranulin binds to both TLR9 and CpG oligonucleotides (CpG-ODNs) in immune cells and endosomes, favoring TLR9 and CpG-ODNs interaction and potentiating the innate immune response to bacterial infections [9]. Notably, it has been reported that progranulin can activate other receptor-tyrosine kinases, including members of the Eph family, such as EphA4 and EphB2 [21][32], EGFR [21][32][39], ErbB2 [21] and RYK [39]. However, it is not known whether progranulin activates these receptors by direct binding or indirectly by activating functional cross-talks.

The domains responsible for progranulin interaction with some of its membrane binding partners have been characterized [16] and referenced herein. Progranulin interaction with TNFR1, TNFR2 and DR3 is mediated by the granulin modules A, C and F and the linkers P3, P4 and P5, while domains A, C, D and E allow the interaction with TLR9 and CpG-ODNs [16]. Progranulin binds to sortilin through the last three amino acids in its C-terminal (QLL) [40]. Multiple granulin domains, mostly granulins D and E, bind to the linker region connecting saposins B and C in the prosaposin molecule [41]. On the receptors side, the domains involved in progranulin binding are known only for TNF receptors and DR3 [42]. Indeed, it has been demonstrated that progranulin binds the cysteine-rich domains (CRD)2 and 3 of TNF receptors [42]. Considering that both CRD and EGF-like domains can bind to progranulin and that at least one of these domains is part of the extracellular region of all known progranulin-binding receptors, it is possible that CRD and EGF-like domains are more likely involved in progranulin interactions with other receptors than TNFR.

2.3. Progranulin Binding Partners Belonging to the ER/Golgi/Lysosome Network

Intracellular progranulin mostly localizes in the endoplasmic reticulum and lysosomes [43]. In the ER, progranulin binding partners include several chaperones, such as endoplasmic reticulum protein (ERp)5, ERp57 and ERp72, heat-shock protein 70 (HSP70), GRP94, binding immunoglobulin protein (BiP), calreticulin and protein disulfide isomerase (PDI) [43] and references therein. It is believed that these chaperones assist in progranulin folding and secretion [43]. In lysosomes, progranulin acts as a co-chaperone by interacting with various hydrolases, such as glucocerebrosidase (GCase), cathepsin D (CSTD) and β-hexosaminidase (HexA) [43]. The relevance of progranulin function as a lysosomal protein is exemplified by the phenotypes associated with progranulin loss, as reviewed by Chitramuthu et al. [17]. Indeed, progranulin deficiency is usually associated with lysosomal disfunctions with progranulin homozygous loss causing cerebroid lipofuscinosis, a severe lysosomal disorder [17]. On the contrary, *GRN* haploinsufficiency leads to frontotemporal

dementia (FTD), a disorder characterized by the neurodegeneration of the frontal and temporal lobes, and lysosome disfunction associated with the presence of neuronal inclusions containing fragments of ubiquitinated TDP-43 [17].

References

1. Diaz-Cueto, L.; Stein, P.; Jacobs, A.; Schultz, R.M.; Gerton, G.L. Modulation of mouse preimplantation embryo development by acrogranin (epithelin/granulin precursor). Dev. Biol. 2000, 217, 406–418.
2. Qin, J.; Diaz-Cueto, L.; Schwarze, J.E.; Takahashi, Y.; Imai, M.; Isuzugawa, K.; Yamamoto, S.; Chang, K.T.; Gerton, G.L.; Imakawa, K. Effects of progranulin on blastocyst hatching and subsequent adhesion and outgrowth in the mouse. Biol. Reprod. 2005, 73, 434–442.
3. Desmarais, J.A.; Cao, M.; Bateman, A.; Murphy, B.D. Spatiotemporal expression pattern of progranulin in embryo implantation and placenta formation suggests a role in cell proliferation, remodeling, and angiogenesis. Reproduction 2008, 136, 247–257.
4. He, Z.; Bateman, A. Progranulin (granulin-epithelin precursor, PC-cell-derived growth factor, acrogranin) mediates tissue repair and tumorigenesis. J. Mol. Med. 2003, 81, 600–612.
5. Zhao, Y.P.; Tian, Q.Y.; Frenkel, S.; Liu, C.J. The promotion of bone healing by progranulin, a downstream molecule of BMP-2, through interacting with TNF/TNFR signaling. Biomaterials 2013, 34, 6412–6421.
6. Toh, H.; Cao, M.; Daniels, E.; Bateman, A. Expression of the growth factor progranulin in endothelial cells influences growth and development of blood vessels: A novel mouse model. PLoS ONE 2013, 8, e64989.
7. Tang, W.; Lu, Y.; Tian, Q.Y.; Zhang, Y.; Guo, F.J.; Liu, G.Y.; Syed, N.M.; Lai, Y.; Lin, E.A.; Kong, L.; et al. The growth factor progranulin binds to TNF receptors and is therapeutic against inflammatory arthritis in mice. Science 2011, 332, 478–484.
8. Yin, F.; Banerjee, R.; Thomas, B.; Zhou, P.; Qian, L.; Jia, T.; Ma, X.; Ma, Y.; Iadecola, C.; Beal, M.F.; et al. Exaggerated inflammation, impaired host defense, and neuropathology in progranulin-deficient mice. J. Exp. Med. 2010, 207, 117–128.
9. Park, B.; Buti, L.; Lee, S.; Matsuwaki, T.; Spooner, E.; Brinkmann, M.M.; Nishihara, M.; Ploegh, H.L. Granulin is a soluble cofactor for toll-like receptor 9 signaling. Immunity 2011, 34, 505–513.
10. Van Damme, P.; Van Hoecke, A.; Lambrechts, D.; Vanacker, P.; Bogaert, E.; van Swieten, J.; Carmeliet, P.; Van Den Bosch, L.; Robberecht, W. Progranulin functions as a neurotrophic factor to regulate neurite outgrowth and enhance neuronal survival. J. Cell Biol. 2008, 181, 37–41.
11. Ryan, C.L.; Baranowski, D.C.; Chitramuthu, B.P.; Malik, S.; Li, Z.; Cao, M.; Minotti, S.; Durham, H.D.; Kay, D.G.; Shaw, C.A.; et al. Progranulin is expressed within motor neurons and promotes neuronal cell survival. BMC Neurosci. 2009, 10, 130.
12. Martens, L.H.; Zhang, J.; Barmada, S.J.; Zhou, P.; Kamiya, S.; Sun, B.; Min, S.W.; Gan, L.; Finkbeiner, S.; Huang, E.J.; et al. Progranulin deficiency promotes neuroinflammation and neuron loss following toxin-induced injury. J. Clin. Investig. 2022, 132, 157161.
13. Hu, F.; Padukkavidana, T.; Vaegter, C.B.; Brady, O.A.; Zheng, Y.; Mackenzie, I.R.; Feldman, H.H.; Nykjaer, A.; Strittmatter, S.M. Sortilin-mediated endocytosis determines levels of the frontotemporal dementia protein, progranulin. Neuron 2010, 68, 654–667.
14. Tanaka, Y.; Matsuwaki, T.; Yamanouchi, K.; Nishihara, M. Increased lysosomal biogenesis in activated microglia and exacerbated neuronal damage after traumatic brain injury in progranulin-deficient mice. Neuroscience 2013, 250, 8–19.
15. Bateman, A.; Cheung, S.T.; Bennett, H.P.J. A Brief Overview of Progranulin in Health and Disease. Methods Mol. Biol. 2018, 1806, 3–15.
16. Cui, Y.; Hettinghouse, A.; Liu, C.J. Progranulin: A conductor of receptors orchestra, a chaperone of lysosomal enzymes and a therapeutic target for multiple diseases. Cytokine Growth Factor Rev. 2019, 45, 53–64.
17. Chitramuthu, B.P.; Bennett, H.P.J.; Bateman, A. Progranulin: A new avenue towards the understanding and treatment of neurodegenerative disease. Brain 2017, 140, 3081–3104.
18. Baker, M.; Mackenzie, I.R.; Pickering-Brown, S.M.; Gass, J.; Rademakers, R.; Lindholm, C.; Snowden, J.; Adamson, J.; Sadovnick, A.D.; Rollinson, S.; et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 2006, 24, 916–919.
19. Cruts, M.; Gijselinck, I.; van der Zee, J.; Engelborghs, S.; Wils, H.; Pirici, D.; Rademakers, R.; Vandenberghe, R.; Dermaut, B.; Martin, J.J.; et al. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to

chromosome 17q21. Nature 2006, 442, 920–924.

20. Jian, J.; Li, G.; Hettinghouse, A.; Liu, C. Progranulin: A key player in autoimmune diseases. Cytokine 2018, 101, 48–55.
21. Chitramuthu, B.P.; Campos-García, V.R.; Bateman, A. Multiple Molecular Pathways Are Influenced by Progranulin in a Neuronal Cell Model-A Parallel Omics Approach. Front. Neurosci. 2021, 15, 775391.
22. Hoque, M.; Tian, B.; Mathews, M.B.; Pe'ery, T. Granulin and granulin repeats interact with the Tat.P-TEFb complex and inhibit Tat transactivation. J. Biol. Chem. 2005, 280, 13648–13657.
23. Hoque, M.; Young, T.M.; Lee, C.G.; Serrero, G.; Mathews, M.B.; Pe'ery, T. The growth factor granulin interacts with cyclin T1 and modulates P-TEFb-dependent transcription. Mol. Cell Biol. 2003, 23, 1688–1702.
24. Gonzalez, E.M.; Mongiat, M.; Slater, S.J.; Baffa, R.; Iozzo, R.V. A novel interaction between perlecan protein core and progranulin: Potential effects on tumor growth. J. Biol Chem. 2003, 278, 38113–38116.
25. Abella, V.; Pino, J.; Scotece, M.; Conde, J.; Lago, F.; Gonzalez-Gay, M.A.; Mera, A.; Gomez, R.; Mobasheri, A.; Gualillo, O. Progranulin as a biomarker and potential therapeutic agent. Drug Discov. Today 2017, 22, 1557–1564.
26. Xu, K.; Zhang, Y.; Ilalov, K.; Carlson, C.S.; Feng, J.Q.; Di Cesare, P.E.; Liu, C.J. Cartilage oligomeric matrix protein associates with granulin-epithelin precursor (GEP) and potentiates GEP-stimulated chondrocyte proliferation. J. Biol. Chem. 2007, 282, 11347–11355.
27. Kong, L.; Zhao, Y.P.; Tian, Q.Y.; Feng, J.Q.; Kobayashi, T.; Merregaert, J.; Liu, C.J. Extracellular matrix protein 1, a direct targeting molecule of parathyroid hormone-related peptide, negatively regulates chondrogenesis and endochondral ossification via associating with progranulin growth factor. FASEB J. 2016, 30, 2741–2754.
28. Nicholson, A.M.; Finch, N.A.; Almeida, M.; Perkerson, R.B.; van Blitterswijk, M.; Wojtas, A.; Cenik, B.; Rotondo, S.; Inskeep, V.; Almasy, L.; et al. Prosaposin is a regulator of progranulin levels and oligomerization. Nat. Commun. 2016, 7, 11992.
29. Liu, C.; Li, X.X.; Gao, W.; Liu, W.; Liu, D.S. Progranulin-derived Atsttrin directly binds to TNFRSF25 (DR3) and inhibits TNF-like ligand 1A (TL1A) activity. PLoS ONE 2014, 9, e92743.
30. Altmann, C.; Vasic, V.; Hardt, S.; Heidler, J.; Häussler, A.; Wittig, I.; Schmidt, M.H.H.; Tegeder, I. Progranulin promotes peripheral nerve regeneration and reinnervation: Role of notch signaling. Mol. Neurodegener. 2016, 11, 69.
31. Baladron, V.; Ruiz-Hidalgo, M.J.; Bonvini, E.; Gubina, E.; Notario, V.; Laborda, J. The EGF-like homeotic protein dlk affects cell growth and interacts with growth-modulating molecules in the yeast two-hybrid system. Biochem. Biophys. Res. Commun. 2002, 291, 193–204.
32. Neill, T.; Buraschi, S.; Goyal, A.; Sharpe, C.; Natkanski, E.; Schaefer, L.; Morrione, A.; Iozzo, R.V. EphA2 is a functional receptor for the growth factor progranulin. J. Cell Biol. 2016, 215, 687–703.
33. Zhou, X.; Sun, L.; Bastos de Oliveira, F.; Qi, X.; Brown, W.J.; Smolka, M.B.; Sun, Y.; Hu, F. Prosaposin facilitates sortilin-independent lysosomal trafficking of progranulin. J. Cell Biol. 2015, 210, 991–1002.
34. Terryn, J.; Verfaillie, C.M.; Van Damme, P. Tweaking Progranulin Expression: Therapeutic Avenues and Opportunities. Front. Mol. Neurosci. 2021, 14, 713031.
35. Etemadi, N.; Webb, A.; Bankovacki, A.; Silke, J.; Nachbur, U. Progranulin does not inhibit TNF and lymphotoxin-alpha signalling through TNF receptor 1. Immunol. Cell Biol. 2013, 91, 661–664.
36. Chen, X.; Chang, J.; Deng, Q.; Xu, J.; Nguyen, T.A.; Martens, L.H.; Cenik, B.; Taylor, G.; Hudson, K.F.; Chung, J.; et al. Progranulin does not bind tumor necrosis factor (TNF) receptors and is not a direct regulator of TNF-dependent signaling or bioactivity in immune or neuronal cells. J. Neurosci. 2013, 33, 9202–9213.
37. Lang, I.; Fullsack, S.; Wajant, H. Lack of Evidence for a Direct Interaction of Progranulin and Tumor Necrosis Factor Receptor-1 and Tumor Necrosis Factor Receptor-2 From Cellular Binding Studies. Front. Immunol. 2018, 9, 793.
38. Wang, B.C.; Liu, H.; Talwar, A.; Jian, J. New discovery rarely runs smooth: An update on progranulin/TNFR interactions. Protein Cell 2015, 6, 792–803.
39. Ventura, E.; Xie, C.; Buraschi, S.; Belfiore, A.; Iozzo, R.V.; Giordano, A.; Morrione, A. Complexity of progranulin mechanisms of action in mesothelioma. J. Exp. Clin. Cancer Res. 2022, 41, 333.
40. Zheng, Y.; Brady, O.A.; Meng, P.S.; Mao, Y.; Hu, F. C-terminus of progranulin interacts with the beta-propeller region of sortilin to regulate progranulin trafficking. PLoS ONE 2011, 6, e21023.
41. Zhou, X.; Sullivan, P.M.; Sun, L.; Hu, F. The interaction between progranulin and prosaposin is mediated by granulins and the linker region between saposin B and C. J. Neurochem. 2017, 143, 236–243.
42. Jian, J.; Zhao, S.; Tian, Q.; Gonzalez-Gugel, E.; Mundra, J.J.; Uddin, S.M.; Liu, B.; Richbourgh, B.; Brunetti, R.; Liu, C.J. Progranulin directly binds to the CRD2 and CRD3 of TNFR extracellular domains. FEBS Lett. 2013, 587, 3428–

3436.

43. Paushter, D.H.; Du, H.; Feng, T.; Hu, F. The lysosomal function of progranulin, a guardian against neurodegeneration. Acta Neuropathol. 2018, 136, 1–17.