Anti-Cancer Effects of Atrial Natriuretic Peptides

Subjects: Endocrinology & Metabolism | Immunology

Contributor: Huafeng Fu , Jian Zhang , Qinbo Cai , Yulong He , Dongjie Yang

The atrial natriuretic peptide (ANP), a cardiovascular hormone, plays a pivotal role in the homeostatic control of blood pressure, electrolytes, and water balance and is approved to treat congestive heart failure. In addition, there is a growing realization that ANPs might be related to immune response and tumor growth. The anti-inflammatory and immune-modulatory effects of ANPs in the tissue microenvironment are mediated through autocrine or paracrine mechanisms, which further suppress tumorigenesis. In cancers, ANPs show anti-proliferative effects through several molecular pathways. Furthermore, ANPs attenuate the side effects of cancer therapy. Therefore, ANPs act on several hallmarks of cancer, such as inflammation, angiogenesis, sustained tumor growth, and metastasis.

atrial natriuretic peptide   inflammation   anti-cancer agent

1. Modulation of Inflammation and Anti-Tumor Effects

Innate and adaptive immunity either promotes or inhibits various aspects of tumor development, as well as regulates responses to anti-cancer therapy [1]. The relationship between the immune system and carcinogenesis, as well as response to anti-tumor therapy, is intimate. The documenting of leukocytes within tumors, as observed in the 19th century by Rudolf Virchow, first linked cancer with inflammation [2]. This hypothesis gained clear evidence hereafter, and tumor-associated inflammation has been recognized as a hallmark of cancer [3]. Chronic inflammation drives tumorigenesis and promotes tumor progression and metastasis, as well as drug resistance [4].

ANPs can counteract the occurrence of inflammation and inflammasome activation in the TME to inhibit tumor development. Persistent inflammation is a potent risk factor for neoplastic transformation [5]. ANPs were shown to inhibit LPS-induced pro-inflammatory enzyme expression, NF-κB activation, and pro-inflammatory cytokine secretion [6]. Meanwhile, NPRA-disrupted mice have shown higher expressions of pro-inflammatory cytokines, such as TNF-α, IL-6, and TGF-β1 [7][8]. Subramanian et al. reported that 4 weeks of ANP treatment significantly inhibited skin cancer development in a mouse model of skin cancer. Significant reductions in the NF-κB activation levels, mast cell infiltration numbers, and MMP-2/9 levels in the skin tissues of mice treated with ANPs were observed, while the changes in serum lactate dehydrogenase-4, C-reactive protein, and enzymatic antioxidants (superoxide dismutase and catalase activities) were close to normal [9]. Chronic inflammation promotes prostate cancer progress and drug resistance [10]. Prostate cancer cells secrete extracellular vesicles (EVs) loaded with pro-inflammatory molecules to modify the tumor microenvironment and promote tumor progression [11]. Mezzasoma et al. reported that ANPs phosphorylated the NLRP3 receptor through the p38-MAPK pathway and then inhibited the

inflammasome activation and IL-β maturation in PC3 cells, as well as reversing the inflammatory phenotypes of normal cells induced by EVs from PC3 cells [12].

ANPs are a potent agent to inhibit perioperative systemic inflammation and postoperative cancer recurrence. If the primary solid tumor meets surgical indications and the patient's physical condition permits, the surgical removal of tumors remains a mainstay attempt to cure patients. However, surgical trauma not only provokes the detachment of cancer cells, leading to an increase in circulating tumor cell (CTC) count, but it also causes a severe systemic inflammatory reaction that speeds up the adhesion of CTCs to the endothelium of distant organs [13][14][15][16]. This is an important step in hematogenous metastases. Nojiri et al. reported that, in a large-scale observational clinical study, the perioperative administration of low-dose human ANPs reduced inflammatory responses and postoperative cardiopulmonary complications in patients receiving surgical treatment for lung cancer [17][18]. Interestingly, patients treated with ANPs had longer 2-year relapse-free survival times [19]. In the lungs of tumor-bearing mice, a significant inactivation of the ANP–NPRA pathway was noticed at the pre-metastatic niche, and ANP treatment downregulated pre-metastatic niche factors, thus preventing lung metastasis [19]. Therefore, the ANP–NPRA pathway may have potential therapeutic value in preventing the pre-metastatic niche formation of solid cancers.

NPRA signaling provides a critical link between inflammation and tumorigenesis. ANPs exert biological effects through interacting with two specific plasma membrane receptors: NPRA and NPRC. Kong et al. reported that the NH (2)-terminal peptide of the ANP prohormone NP73-102 exerted robust anti-inflammatory and anti-tumor effects by blocking the expression of NPRA [20]. In addition, in an endothelial-sprouting assay, an NPRA antagonist reduced NPRA expression and inhibited inflammation-induced angiogenesis by downregulating vascular endothelial growth factor (VEGF) and chemokine (C-X-C motif) receptor 4 (CXCR4). The accumulation of cancer-associated fibroblasts, endothelial cells, and macrophages decreased in an NPRA-disrupted mouse tumor microenvironment compared to WT mice, suggesting that NPRA signaling promoted tumor–stroma interaction. In addition, the absence of NPRA caused mesenchymal stem cells (MSCs) to fail to migrate to the TME. In contrast, significant increases in angiogenesis and tumorigenesis were noticed in NPRA-disrupted mice when co-implanting tumor cells with MSCs. These findings suggest that CXCR4 expression and stromal-derived factor 1α secretion are dependent on NPRA signaling [21]. Thus, NPRA signaling may be a potential therapeutic target for inflammation-associated tumorigenesis.

2. RAS-MEK1/2-ERK1/2 Kinase Cascade

Oncogenic mutated forms of Ras are detected in approximately 15% of cancers, and ERK hyperactivation can be seen in nearly one-third of human cancers, leading to deregulation of the RAS-mitogen-activated protein kinase (MEK)-extracellular-signal-regulated kinase (ERK) signaling pathway [22]. Sun et al. reported that ANP and LANP treatment could effectively inhibit the conversion of the RAS-GDP signal to the RAS-GTP signal in prostate cancer cells [23]. In addition, ANPs could suppress the activation of MEK1/2 and ERK1/2 in prostate cancer cells, and the inhibitory effect could be largely abolished by the cGMP antibody [24]. EGF and insulin were shown to stimulate

ERK 1/2 kinases through mediating conversion of RAS-GDP to active RAS-GTP [25]. What is more, ANPs could block the activation of RAS and ERK 1/2 by mitogens such as insulin and epidermal growth factor (EGF) [26].

3. ANPs Interact with Other Transcription Factors and Cell Signaling Systems

3.1. VEGF

Tumor cells and the surrounding stroma can secrete VEGF [27]. The overexpression of VEGF is related to tumor vascular density, invasiveness, metastasis, recurrence, and prognosis, and the blockading of VEGF may lead to a regression in the vascular network and the containment of tumor growth [28][29]. Given the fact that vascular endothelium cells express high levels of NPRA and that cell exposure to ANPs can counteract VEGF-induced endothelial cell proliferation signals, the ANP/NPR1 signal plays a critical role in the regulation of endothelial cell functional activity and proliferation [30]. Levin et al. showed that ANP inhibited the activation of several key signaling molecules, including ERK, JNK, and p38 members of the MAP kinase family, that were important for VEGF-induced angiogenesis [31]. ANPs could significantly block VEGF-induced endothelial cell proliferation and migration [32]. Nguyen et al. reported that ANPs could inhibit VEGF and VEGF receptor 2 in human cancer cell lines [33]. In addition, Mao et al. showed that ANPs combined with glipizide significantly suppressed breast cancer growth by inhibiting tumor-induced angiogenesis [34]. Moreover, Nakao et al. showed that high NPRA expression in tongue squamous cell carcinoma had a poorer prognosis, and NPRA was related to the expressions of VEGFA and VEGFC, which were associated with the invasion potential of tongue squamous cell carcinoma [35].

3.2. Wnt/β-Catenin Signaling Cascade

The dysregulation of the Wnt/β-catenin signal caused by mutations or epigenetic changes contributes to the initiation and development of various human cancers [36]. ANPs downregulated β-catenin expression and caused a significant downregulation of c-Myc and cyclin D-1 transcriptions [37]. An acidic microenvironment has been identified as critical factor for the development of cancer. ANPs can modify the pH by inhibiting or stimulating NHE-1 [38][39]. Serafino et al. showed that ANPs induced NHE-1 inactivation, leading to an increase in intracellular acidity, inhibiting Wnt/β-catenin signaling through a frizzled-mediated activation that was on the upstream of the cascade, simultaneously [40].

3.3. JNK and JAK/STATs Signaling

The c-JUN N-terminal kinase (JNK) pathway is involved in a range of pathological conditions, including inflammation and cancer progression [41]. ANPs could reduce the expression of JNK2 in human prostate adenocarcinoma and small-cell lung cancer cells [42]. The signal transducer and activator of transcription (STAT3) signal is constitutively activated during cancer development and is associated with different hallmarks of cancer [43]. Lane et al. showed that ANPs inhibited the expression of STAT3 in human cancer cells [37].

3.4. ROS Production

Cancer cells show higher level of ROS than normal cells, partly due to high metabolic activity, peroxisomal activity, and mitochondrial dysfunction, which contributes to tumorigenesis, tumor progression, and metastasis, as well as drug resistance [44][45][46]. When the levels of ROS fluctuate, cancer cells more easily reach their oxidative stress thresholds compare to normal cells, resulting in oxidative-stress-induced cell death [47][48]. In hepG2 cells, increased expression of ANP-inhibited cell growth was seen through the upregulation of NPRC [49]. Baldini et al. showed that, in ANP-treated HepG2 cells, a significant decrease in pHi, enhancement in the PLD activity, and an increase in the ROS level were observed simultaneously [50]. Furthermore, ANP-induced ROS generation via the involvement of the NADPH oxidase system subsequently inhibited the caspase-3 enzyme and switched HepG2 cell death from apoptosis to necrosis [51]. However, Kiemers et al. showed that ANP had a cytoprotective effect on liver cells after ischemia reperfusion injury [52], which might be attributed to the differences between tumor cells and normal cells in terms of threshold signal, NPR-C expression, and intracellular ROS level [53].

3.5. KCNQ1 Expression

Plasma K^+ channels are important in tumor cell proliferation [54][55]. Zhang et al. showed that ANPs played a pleiotropic role in gastric cancer cell proliferation, and the physiological concentration of ANPs upregulated the expression of the potassium-voltage-gated channel and KQT-like subfamily member 1 (KCNQ1) to promote AGS cell proliferation, while the pharmacological concentration of ANP significantly downregulated KCNQ1 expression to inhibit AGS proliferation [56]. Furthermore, the knockdown of NPRA decreased the protein level of KCNQ1 and the voltage-gated outward K^+ current [57].

3.6. MMP9 Expression

The dysregulation of MMP9 is related to several hallmarks of cancer, including inflammation, angiogenesis, tumor growth, and metastasis [58]. Li et al. reported that ANPs significantly inhibited gastric cancer cell migration and invasion by downregulating the hedgehog-signaling-mediated activation of MMP9 [59]. In vivo, ANP treatment significantly reduced NF-κB activation levels, mast cell infiltration numbers, and MMP2/9 levels in the skin tissues of a skin cancer mouse model [9] (**Figure 1**).
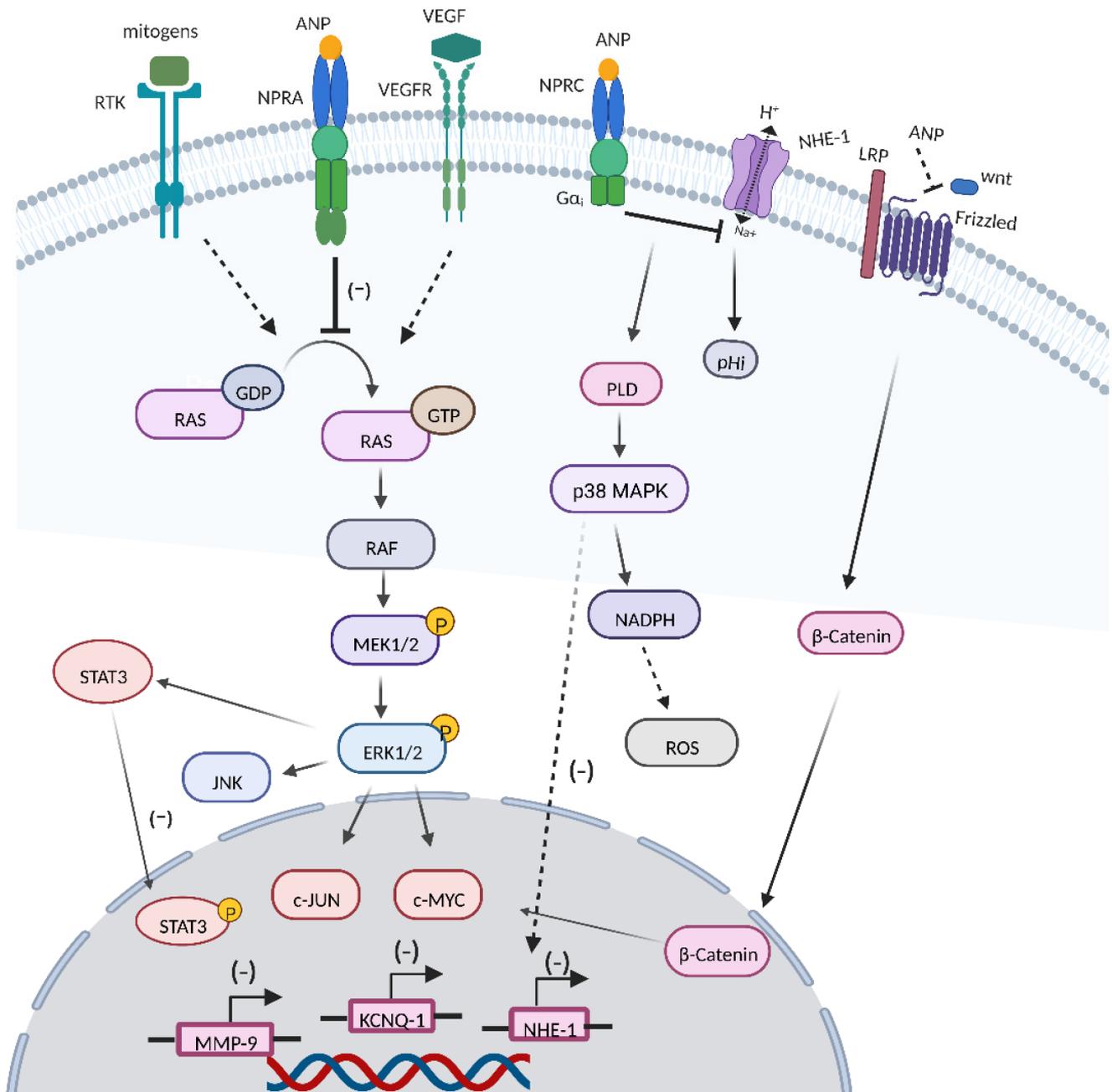
Figure 1. Roles of ANPs in cancer. ANPs exert antineoplastic potential by inhibiting the conversion of GDP-RAS to GTP-RAS, the RAS-MEK1/2-ERK1/2 kinase cascade, and cross-talk between the RAS-MEK1/2-ERK1/2 kinase cascade and VEGF, β-catenin, JNK, WNT, and STAT3. In addition, ANPs also modulate inflammation, ROS production, KCNQ1, and MMP9 expression.

References

1. Shalapour, S.; Karin, M. Immunity, inflammation, and cancer: An eternal fight between good and evil. J. Clin. Investig. 2015, 125, 3347–3355.

2. Balkwill, F.; Mantovani, A. Inflammation and cancer: Back to Virchow? Lancet 2001, 357, 539–545.

3. Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: The next generation. Cell 2011, 144, 646–674.

4. Grivennikov, S.I.; Greten, F.R.; Karin, M. Immunity, inflammation, and cancer. Cell 2010, 140, 883–899.

5. Khansari, N.; Shakiba, Y.; Mahmoudi, M. Chronic inflammation and oxidative stress as a major cause of age-related diseases and cancer. Recent Pat. Inflamm. Allergy Drug Discov. 2009, 3, 73–80.

6. Vollmar, A.M. The role of atrial natriuretic peptide in the immune system. Peptides 2005, 26, 1086–1094.

7. Vellaichamy, E.; Khurana, M.L.; Fink, J.; Pandey, K.N. Involvement of the NF-kappa B/matrix metalloproteinase pathway in cardiac fibrosis of mice lacking guanylyl cyclase/natriuretic peptide receptor A. J. Biol. Chem. 2005, 280, 19230–19242.

8. Vellaichamy, E.; Kaur, K.; Pandey, K.N. Enhanced activation of pro-inflammatory cytokines in mice lacking natriuretic peptide receptor-A. Peptides 2007, 28, 893–899.

9. Subramanian, V.; Vellaichamy, E. Atrial natriuretic peptide (ANP) inhibits DMBA/croton oil induced skin tumor growth by modulating NF-κB, MMPs, and infiltrating mast cells in swiss albino mice. Eur. J. Pharmacol. 2014, 740, 388–397.

10. Archer, M.; Dogra, N.; Kyprianou, N. Inflammation as a Driver of Prostate Cancer Metastasis and Therapeutic Resistance. Cancers 2020, 12, 2984.

11. Mezzasoma, L.; Costanzi, E.; Scarpelli, P.; Talesa, V.N.; Bellezza, I. Extracellular Vesicles from Human Advanced-Stage Prostate Cancer Cells Modify the Inflammatory Response of Microenvironment-Residing Cells. Cancers 2019, 11, 1276.

12. Mezzasoma, L.; Talesa, V.N.; Costanzi, E.; Bellezza, I. Natriuretic Peptides Regulate Prostate Cells Inflammatory Behavior: Potential Novel Anticancer Agents for Prostate Cancer. Biomolecules 2021, 11, 794.

13. Funaki, S.; Sawabata, N.; Nakagiri, T.; Shintani, Y.; Inoue, M.; Kadota, Y.; Minami, M.; Okumura, M. Novel approach for detection of isolated tumor cells in pulmonary vein using negative selection method: Morphological classification and clinical implications. Eur. J. Cardiothorac. Surg. 2011, 40, 322–327.

14. Giavazzi, R.; Foppolo, M.; Dossi, R.; Remuzzi, A. Rolling and adhesion of human tumor cells on vascular endothelium under physiological flow conditions. J. Clin. Investig. 1993, 92, 3038–3044.

15. Koch, M.; Kienle, P.; Hinz, U.; Antolovic, D.; Schmidt, J.; Herfarth, C.; von Knebel Doeberitz, M.; Weitz, J. Detection of hematogenous tumor cell dissemination predicts tumor relapse in patients

undergoing surgical resection of colorectal liver metastases. Ann. Surg. 2005, 241, 199–205.

16. McDonald, B.; Spicer, J.; Giannais, B.; Fallavollita, L.; Brodt, P.; Ferri, L.E. Systemic inflammation increases cancer cell adhesion to hepatic sinusoids by neutrophil mediated mechanisms. Int. J. Cancer 2009, 125, 1298–1305.

17. Nojiri, T.; Inoue, M.; Yamamoto, K.; Maeda, H.; Takeuchi, Y.; Funakoshi, Y.; Okumura, M. Effects of low-dose human atrial natriuretic peptide for preventing post-operative cardiopulmonary complications in elderly patients undergoing pulmonary resection for lung cancer. Eur. J. Cardiothorac. Surg. 2012, 41, 1330–1334.

18. Nojiri, T.; Yamamoto, K.; Maeda, H.; Takeuchi, Y.; Funakoshi, Y.; Inoue, M.; Okumura, M. Effect of low-dose human atrial natriuretic peptide on postoperative atrial fibrillation in patients undergoing pulmonary resection for lung cancer: A double-blind, placebo-controlled study. J. Thorac. Cardiovasc. Surg. 2012, 143, 488–494.

19. Nojiri, T.; Arai, M.; Suzuki, Y.; Kumazoe, M.; Tokudome, T.; Miura, K.; Hino, J.; Hosoda, H.; Miyazato, M.; Okumura, M.; et al. Transcriptome analysis reveals a role for the endothelial ANP-GC-A signaling in interfering with pre-metastatic niche formation by solid cancers. Oncotarget 2017, 8, 65534–65547.

20. Kong, X.; Wang, X.; Xu, W.; Behera, S.; Hellermann, G.; Kumar, A.; Lockey, R.F.; Mohapatra, S.; Mohapatra, S.S. Natriuretic peptide receptor a as a novel anticancer target. Cancer Res. 2008, 68, 249–256.

21. Mallela, J.; Ravi, S.; Jean Louis, F.; Mulaney, B.; Cheung, M.; Sree Garapati, U.; Chinnasamy, V.; Wang, C.; Nagaraj, S.; Mohapatra, S.S.; et al. Natriuretic peptide receptor A signaling regulates stem cell recruitment and angiogenesis: A model to study linkage between inflammation and tumorigenesis. Stem Cells 2013, 31, 1321–1329.

22. Davies, H.; Bignell, G.R.; Cox, C.; Stephens, P.; Edkins, S.; Clegg, S.; Teague, J.; Woffendin, H.; Garnett, M.J.; Bottomley, W.; et al. Mutations of the BRAF gene in human cancer. Nature 2002, 417, 949–954.

23. Sebolt-Leopold, J.S. Advances in the development of cancer therapeutics directed against the RAS-mitogen-activated protein kinase pathway. Clin. Cancer Res. 2008, 14, 3651–3656.

24. Sun, Y.; Eichelbaum, E.J.; Wang, H.; Vesely, D.L. Atrial natriuretic peptide and long acting natriuretic peptide inhibit MEK 1/2 activation in human prostate cancer cells. Anticancer Res. 2007, 27, 3813–3818.

25. Medema, R.H.; de Vries-Smits, A.M.; van der Zon, G.C.; Maassen, J.A.; Bos, J.L. Ras activation by insulin and epidermal growth factor through enhanced exchange of guanine nucleotides on p21ras. Mol. Cell. Biol. 1993, 13, 155–162.

26. Vesely, D.L. Natriuretic peptides' metabolic targets for treatment of cancer. J. Investig. Med. 2013, 61, 816–822.

27. Apte, R.S.; Chen, D.S.; Ferrara, N. VEGF in Signaling and Disease: Beyond Discovery and Development. Cell 2019, 176, 1248–1264.

28. Kerbel, R.S. Tumor angiogenesis. N. Engl. J. Med. 2008, 358, 2039–2049.

29. Ribatti, D.; Solimando, A.G.; Pezzella, F. The Anti-VEGF(R) Drug Discovery Legacy: Improving Attrition Rates by Breaking the Vicious Cycle of Angiogenesis in Cancer. Cancers 2021, 13, 3433.

30. Pedram, A.; Razandi, M.; Levin, E.R. Natriuretic peptides suppress vascular endothelial cell growth factor signaling to angiogenesis. Endocrinology 2001, 142, 1578–1586.

31. Levin, E.R.; Gardner, D.G.; Samson, W.K. Natriuretic peptides. N. Engl. J. Med. 1998, 339, 321–328.

32. Kook, H.; Itoh, H.; Choi, B.S.; Sawada, N.; Doi, K.; Hwang, T.J.; Kim, K.K.; Arai, H.; Baik, Y.H.; Nakao, K. Physiological concentration of atrial natriuretic peptide induces endothelial regeneration in vitro. Am. J. Physiol. Heart Circ. Physiol. 2003, 284, H1388–H1397.

33. Nguyen, J.P.; Frost, C.D.; Lane, M.L.; Skelton, W.I.; Skelton, M.; Vesely, D.L. Novel dual inhibitors of vascular endothelial growth factor and VEGFR2 receptor. Eur. J. Clin. Investig. 2012, 42, 1061–1067.

34. Mao, G.; Zheng, S.; Li, J.; Liu, X.; Zhou, Q.; Cao, J.; Zhang, Q.; Zheng, L.; Wang, L.; Qi, C. Glipizide Combined with ANP Suppresses Breast Cancer Growth and Metastasis by Inhibiting Angiogenesis through VEGF/VEGFR2 Signaling. Anticancer Agents Med. Chem. 2022, 22, 1735–1741.

35. Nakao, Y.; Yamada, S.; Yanamoto, S.; Tomioka, T.; Naruse, T.; Ikeda, T.; Kurita, H.; Umeda, M. Natriuretic peptide receptor A is related to the expression of vascular endothelial growth factors A and C, and is associated with the invasion potential of tongue squamous cell carcinoma. Int. J. Oral Maxillofac. Surg. 2017, 46, 1237–1242.

36. Barzegar, B.A.; Talaie, Z.; Jusheghani, F.; Łos, M.J.; Klonisch, T.; Ghavami, S. Wnt and PI3K/Akt/mTOR Survival Pathways as Therapeutic Targets in Glioblastoma. Int. J. Mol. Sci. 2022, 23, 1353.

37. Vesely, D.L. Cardiac hormones for the treatment of cancer. Endocr. Relat. Cancer 2013, 20, R113–R125.

38. Kanda, F.; Sarnacki, P.; Arieff, A.I. Atrial natriuretic peptide inhibits amiloride-sensitive sodium uptake in rat brain. Am. J. Physiol. 1992, 263 Pt 2, R279–R283.

39. Ricci, R.; Baldini, P.; Bogetto, L.; De Vito, P.; Luly, P.; Zannetti, A.; Incerpi, S. Dual modulation of Na/H antiport by atrial natriuretic factor in rat aortic smooth muscle cells. Am. J. Physiol. 1997,

273 Pt 1, C643–C652.

40. Serafino, A.; Moroni, N.; Psaila, R.; Zonfrillo, M.; Andreola, F.; Wannenes, F.; Mercuri, L.; Rasi, G.; Pierimarchi, P. Anti-proliferative effect of atrial natriuretic peptide on colorectal cancer cells: Evidence for an Akt-mediated cross-talk between NHE-1 activity and Wnt/β-catenin signaling. Biochim. Biophys. Acta 2012, 1822, 1004–1018.

41. Kumar, A.; Singh, U.K.; Kini, S.G.; Garg, V.; Agrawal, S.; Tomar, P.K.; Pathak, P.; Chaudhary, A.; Gupta, P.; Malik, A. JNK pathway signaling: A novel and smarter therapeutic targets for various biological diseases. Future Med. Chem. 2015, 7, 2065–2086.

42. Vesely, D.L. Heart Peptide Hormones: Adjunct and Primary Treatments of Cancer. Anticancer Res. 2016, 36, 5693–5700.

43. Yu, H.; Lee, H.; Herrmann, A.; Buettner, R.; Jove, R. Revisiting STAT3 signalling in cancer: New and unexpected biological functions. Nat. Rev. Cancer 2014, 14, 736–746.

44. Galadari, S.; Rahman, A.; Pallichankandy, S.; Thayyullathil, F. Reactive oxygen species and cancer paradox: To promote or to suppress? Free Radic. Biol. Med. 2017, 104, 144–164.

45. Tang, F.; Liu, S.; Li, Q.Y.; Yuan, J.; Li, L.; Wang, Y.; Yuan, B.F.; Feng, Y.Q. Location analysis of 8-oxo-7,8-dihydroguanine in DNA by polymerase-mediated differential coding. Chem. Sci. 2019, 10, 4272–4281.

46. Tang, F.; Yuan, J.; Yuan, B.F.; Wang, Y. DNA-Protein Cross-Linking Sequencing for Genome-Wide Mapping of Thymidine Glycol. J. Am. Chem. Soc. 2022, 144, 454–462.

47. Trachootham, D.; Alexandre, J.; Huang, P. Targeting cancer cells by ROS-mediated mechanisms: A radical therapeutic approach? Nat. Rev. Drug Discov. 2009, 8, 579–591.

48. NavaneethaKrishnan, S.; Rosales, J.L.; Lee, K.Y. Targeting Cdk5 for killing of breast cancer cells via perturbation of redox homeostasis. Oncoscience 2018, 5, 152–154.

49. Rashed, H.M.; Sun, H.; Patel, T.B. Atrial natriuretic peptide inhibits growth of hepatoblastoma (HEP G2) cells by means of activation of clearance receptors. Hepatology 1993, 17, 677–684.

50. Baldini, P.M.; De Vito, P.; Vismara, D.; Bagni, C.; Zalfa, F.; Minieri, M.; Di Nardo, P. Atrial natriuretic peptide effects on intracellular pH changes and ROS production in HEPG2 cells: Role of p38 MAPK and phospholipase D. Cell. Physiol. Biochem. 2005, 15, 77–88.

51. Baldini, P.M.; De Vito, P.; Antenucci, D.; Vismara, D.; D'Aquilio, F.; Luly, P.; Zalfa, F.; Bagni, C.; Di Nardo, P. Atrial natriuretic peptide induces cell death in human hepatoblastoma (HepG2) through the involvement of NADPH oxidase. Cell Death Differ. 2004, 11 (Suppl. 2), S210–S212.

52. Kiemer, A.K.; Gerbes, A.L.; Bilzer, M.; Vollmar, A.M. The atrial natriuretic peptide and cGMP: Novel activators of the heat shock response in rat livers. Hepatology 2002, 35, 88–94.

53. De Vito, P. Atrial natriuretic peptide: An old hormone or a new cytokine? Peptides 2014, 58, 108–116.

54. Zhanping, W.; Xiaoyu, P.; Na, C.; Shenglan, W.; Bo, W. Voltage-gated K+ channels are associated with cell proliferation and cell cycle of ovarian cancer cell. Gynecol. Oncol. 2007, 104, 455–460.

55. Spitzner, M.; Ousingsawat, J.; Scheidt, K.; Kunzelmann, K.; Schreiber, R. Voltage-gated K+ channels support proliferation of colonic carcinoma cells. FASEB J. 2007, 21, 35–44.

56. Zhang, J.; Zhao, Z.; Zu, C.; Hu, H.; Shen, H.; Zhang, M.; Wang, J. Atrial natriuretic peptide modulates the proliferation of human gastric cancer cells via KCNQ1 expression. Oncol. Lett. 2013, 6, 407–414.

57. Zhang, J.; Qu, J.; Yang, Y.; Li, M.; Zhang, M.; Cui, X.; Zhang, J.; Wang, J. Impact of NPR-A expression in gastric cancer cells. Int. J. Clin. Exp. Med. 2014, 7, 3209–3214.

58. Mondal, S.; Adhikari, N.; Banerjee, S.; Amin, S.A.; Jha, T. Matrix metalloproteinase-9 (MMP-9) and its inhibitors in cancer: A minireview. Eur. J. Med. Chem. 2020, 194, 112260.

59. Li, C.H.; Liu, M.; Pan, L.H.; Sun, Y. ANP reduced Hedgehog signaling-mediated activation of matrix metalloproteinase-9 in gastric cancer cell line MGC-803. Gene 2020, 762, 145044.