International Journal of Multiphysics
Volume 18, No. 3, 2024
ISSN: 1750-9548

Role of Pitutary Adenylated Cyclase Activating Polypeptide in Multiple Myeloma

Arwa Osama Mahmoud El-bayaa[1], Saad Sabry El-Osh[1], Marwa Mohammed Esawy[1], Ahmed Mokhtar Ahmed[1] and Ayman Fathy Abd El-Halim[2]

1 Clinical Pathology Department, Faculty of Medicine, Zagazig University

2 Internal Medicine Department, Faculty of Medicine, Zagazig University

Abstract:

Background: Pituitary adenylate cyclase-activating polypeptide (PACAP) is a multifunctional neuropeptide with immunomodulatory, anti-inflammatory, and cytoprotective effects. Emerging evidence suggests that PACAP may influence tumor biology through regulation of proliferation, angiogenesis, apoptosis, and immune surveillance. In hematological malignancies such as multiple myeloma (MM), where the bone marrow microenvironment plays a critical role in disease progression, PACAP signaling may represent a novel modulatory axis.

Keywords: PACAP, multiple myeloma, neuropeptides, bone marrow microenvironment, immunomodulation, apoptosis.

Introduction:

Multiple myeloma (MM) is a hematological malignancy characterized by the clonal proliferation of plasma cells in the bone marrow, leading to bone lesions, anemia, renal dysfunction, and hypercalcemia **(1).**

Pituitary adenylate cyclase-activating polypeptide (PACAP) belongs to the VIP/PACAP neuropeptide family and exhibits broad biological effects, including anti-inflammatory, antioxidant, and cytoprotective actions, with emerging roles in aging and related diseases **(2).**

Recent clinical studies demonstrated that PACAP-38 plasma levels are significantly reduced in MM patients compared to healthy individuals, and higher PACAP levels were associated with deeper therapeutic responses and longer survival outcomes **(3).**

In solid tumor models, PACAP38 was shown to enhance the effects of irradiation by suppressing cancer cell proliferation through SOX6 activation and inhibition of Wnt/β-catenin signaling, suggesting its broader antineoplastic potential **(4).**

For a long time, the presence of disease-related end-organ damage was a diagnostic cornerstone of the definition of symptomatic MM **(5).** However, in 2014, the criteria were modified by the IMWG to include three new biomarkers (more than 60% plasma cells in bone marrow, or more than 100 free light chain ratio, or more than one focal lesion on MRI scan) **(6).**

Biomarkers such as LDH or B2M correlate with tumor burden and have a prognostic role. Furthermore, these conventional biomarkers have several limitations as prognostic markers. At the same time, the incidence and prevalence of MM are steadily increasing, and survival has not improved significantly in recent years. Presumably, survival can be further improved by the earlier detection of transformation from pre-symptomatic stages to symptomatic disease using additional sensitive markers **(7).**

The diagnostic criteria and staging systems proposed by the International Myeloma Working Group (IMWG) remain the key from a disease perspective. However, M-protein is undetectable by serum electrophoresis in 18% of MM cases and by any other diagnostic tool in nearly 3% of patients. B2M levels can also be influenced by several other factors (e.g., renal and liver diseases). This data can lead to misdiagnosis and inaccurate staging. Responses in non-secretory myeloma cannot be assessed and monitored by serum and urine tests, even with most

sensitive serum free light chain (sFLC) assay. Moreover, most of the conventional prognostic biomarkers used thus far are highly correlated with disease burden **(2).**

The expression of extracellular matrix proteins (e.g., ANXA2, LGALS1, LAMB1, ITAG9) is altered at the gene and protein levels in MGUS, SMM, and MM. Therefore, their investigation may be critical for both the prognosis and detection of subsequent drug resistance **(7).**

Investigation of the interactions between the bone marrow microenvironment, consisting of both cellular and non-cellular components, is also crucial for predicting prognosis and drug resistance.

Thus, it will become increasingly important in the future to identify new, reliable biomarkers of malignancy that can be easily and rapidly used in the clinical setting to diagnose disease, determine prognosis, and monitor response to therapy **(8).**

In recent years, significant alterations of PACAP have been detected in human tissues under various physiological and pathological conditions (e.g., neurological disorders: posttraumatic stress disorder; cardiac disorders: cardiomyopathies, acute myocardial infarction; kidney disorders: nephrotic syndrome, nephrectomy), in addition to various malignant disorders. These results suggest a potential role of PACAP in the diagnosis, prognosis, and clinical therapy of certain diseases **(9).**

The PACAP may be one of these promising markers in the future, which may complement conventional diagnostic and prognostic biomarkers. PACAP is a multifunctional neuropeptide with proven anti-inflammatory, antioxidant, and immunomodulatory effects **(2).**

I. Role of PACAP on MM proliferation

A complex network of cytokines and cell adhesion molecules is maintained by bone marrow stromal cells (BMSCs), which regulate the proliferation, survival, and the function of myeloma cells **(10).** Human cytokines have been known to play a major role in the growth and prevention of apoptosis of tumor cells in myeloma patients. Specifically, interleukin 6 (IL-6) promotes multiple myeloma cell growth, survival, and drug resistance **(11)**, whereas vascular endothelial growth factor induces multiple myeloma cell migration **(12).** More precisely, the adhesion of multiple myeloma cells to BMSCs triggers nuclear factor-κβ (NF-κβ)–dependent transcription and secretion of IL-6, whereas inhibition of NF-κβ activity eliminated this response **(13)**. On the other hand, tumor necrosis factor-a (TNF-a) secreted by the multiple myeloma cells in the bone marrow milieu activates NF-κβ, thereby modulating the expression of adhesion molecules on both multiple myeloma cells and BMSCs as well as inducing IL-6 transcription and secretion in BMSCs. Many of these same cytokines also contribute to osteolytic bone destruction. The cells involved in myeloma bone loss make large amounts of cytokines that are capable of stimulating myeloma growth and preventing apoptosis **(14).**

The signaling cascades (Figure **1**) involved in the inhibitory effect of PACAP on IL-6-mediated paracrine stimulation of light chain-secreting myeloma cell growth was mediated through the suppression of p38 mitogen-activated protein kinases (MAPK) as well as modulation of activation of transcription factor NF- κβ **(15).** PACAP suppresses the proliferation of human κ and λ light chain-secreting multiple myeloma–derived cells **(16).**

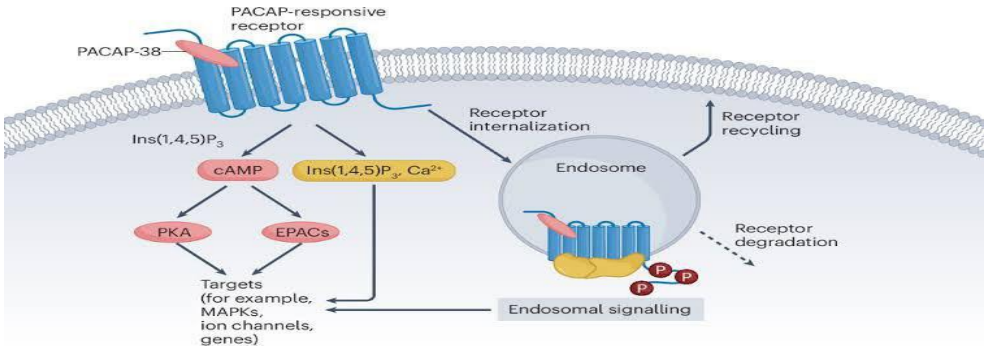

Figure (1): Intracellular signaling pathways activated by pituitary adenylate cyclase-activating polypeptide **(17).**

The addition of PACAP suppressed light chain-producing myeloma cell–stimulated interleukin 6 (IL-6) secretion by the bone marrow stromal cells (BMSCs). A specific antagonist to either the human PACAP-specific receptor or the vasoactive intestinal peptide receptor attenuated the suppressive effect of PACAP on IL-6 production in the adhesion of human multiple myeloma cells to BMSCs **(15).**

The bone marrow microenvironment also confers drug resistance in multiple myeloma cells via at least two different mechanisms: adhesion of multiple myeloma cells to fibronectin confers cell adhesion– mediated drug resistance, associated with induction of p27Kip1 and G1 growth arrest **(18)**, and cytokines (IL-6 and insulin-like growth factor 1) in the bone marrow milieu induce Janus-activated kinase 2 (JAK2)/signal transducers and activators of transcription 3 (STAT3), phosphatidylinositol 3-kinase (PI3K)/a PI3K target (Akt) signaling, or both, which mediates resistance to conventional therapies **(16).** The PACAP inhibits TNF-a synthesis in light chain-secreting myeoma cells and thereby enhances the suppressive effect of PACAP in myeloma growth in the bone marrow microenvironment. The pivotal role of cytokine-mediated multiple myeloma cell growth in the bone marrow milieu prompted us to look into the inhibitory effect of PACAP **(2).**

1. **Effect of PACAP on cellular proliferation of human multiple myeloma cells.**

Li et al. (15) observed that PACAP indeed had an antiproliferative effect on Myeloma tumor cells. Coculture of H929 myeloma cells with PACAP inhibited cell growth dose dependent and maximum inhibition was seen at 10^{-9} mol/L PACAP, which inhibited myeloma proliferation by 45% to 50%. Its suppressive action on the tumor cell was like that displayed by dexamethasone that is considered conventional cytotoxic chemotherapeutic.

PACAP inhibited myeloma cell growth dependently, with a greater suppressive effect on the growth of κ light chain-secreting multiple myeloma cells. Importantly, the addition of IL-6 (20 ng/mL) did not inhibit the suppressive effect of PACAP on the growth of κ -light chain-secreting multiple myeloma cells, although the same dose of IL-6 alone triggered the growth of myeloma cells (**15).**

Effect of PACAP on IL-6 secretion in BMSCs

The IL-6 is a major growth factor for human myeloma cells, and an increase in serum IL-6 could be responsible for the expansion of myeloma cells and the progression of myelomas **(11)**. This effect is triggered by adherence of human multiple myeloma cells to BMSCs. PACAP can inhibit paracrine light chain-secreting multiple myeloma cell growth in the bone marrow milieu and overcome cell adhesion–related drug resistance. The addition of myeloma cells further increased the expression of IL-6 by BMSCs, reaching a maximum level during 24 hours of incubation. The addition of PACAP or dexamethasone to the cocultures suppressed IL-6 secretion dose dependently, and maximum inhibition was seen at 10^{-9} mol/L PACAP, which inhibited IL-6 secretion by 65% to 70% (**15).**

2. **Effect of PACAP receptor antagonists on IL-6 secretion in Multiple myeloma cells adherent to BMSCs.**

The action of a bioactive peptide is generally believed to be mediated by its interaction with the cognate plasma membrane–associated G protein–coupled receptors. The PACAP-specific receptor, PAC1-R, and the PACAP/VIP-shared receptors, VPAC1-Rand VPAC2-R, have been identified on almost every known type of tumor cell **(19).**

At least six human PAC1-R subtypes derived from alternative splicing in the third intracellular loop have been reported The splice variants are characterized by the absence of the third intracellular loop called the short variant or presence of either one or two cassettes of 28 (SV1 or SV2a variant) or 27 (SV2b variant) amino acids. The short variant is the most abundant form in the tissues. To investigate what type of PACAP receptors are expressed in the human BMSCs and light chain-secreting multiple myeloma cells, as well as PBMCs isolated from myeloma patients, the expression of the transcripts for human PAC1, VPAC1, or VPAC2 receptors were examined by RT-PCR analysis using appropriate primers that could specifically discriminate among these three human PACAP/VIP receptors (**15).**

Human BMSCs express all three types of PACAP receptors, including the PAC1-Rshort and SV1 and SV2 variants. However, human H929 myeloma cells expressed the PAC1-Rshort subtype and VPAC1-R, but notVPAC2-R, and PBMCs expressed the PAC1-R short subtype and VPAC2-R, but not VPAC1-R. Either a specific antagonist for PAC1-R, M65, or for VPAC2-R, PG99-485, or antagonist for both PAC1-Rand VPAC2-R, PACAP, attenuated the growth. Suppressive effect of PACAP in terms of the IL-6 production when H929 myeloma cells were adhering to the stromal cells. This suggests that the growth-inhibitory effect of PACAP is mediated through the human PAC1-R short subtype and/or VPAC2-R expressed on the BMSCs **(20).**

3. Effects of PACAP and signaling inhibitors on activations of p2/p44, p38 MAPKs, and NF-KB in human BMSCs adhering to multiple myeloma cells.

The adhesion of human light chain-secreting multiple myeloma cells to BMSCs can activate several signaling pathways, including p42/p44 MAPK and p38 MAPK activations and phosphorylation of NF-κβ dependent transcription **(21).**

PACAP remarkably suppressed the phosphorylation of both ERK1/2, MAPK and p38 MAPK in response to the adhesion of H929 multiple myeloma cells to BMSCs. PACAP does not associate with p42/p44 ERK MAPK. However, H89 plus PDTC slightly attenuated the activity of PACAP on the suppression of IL-6. H89 plus PDTC seems to have rather augmented the suppressive effect of PACAP, although statistically insignificant. These results therefore identify that p38 MAPK–mediated and p50 NF- κβ –mediated signaling cascades are required for the inhibitory effect of PACAP on the adhesion-associated activation of IL-6 transcription and secretion in bone marrow milieu (**15).**

4. Effect of PACAP on the expression of TNF-A mRNA in human multiple myeloma cells.

The TNF-α secretion is significantly higher in those myeloma patients with bone disease. PACAP and dexamethasone have no effect on TNF-α secretion in the bone marrow, but PACAP directly inhibits κ and λ light chain-secreting human multiple myeloma cell proliferation and TNF-α synthesis in myeloma cell cultures. Importantly, PACAP also indirectly inhibits tumor cell growth by suppressing proinflammatory cytokine IL-6 secretion in myeloma and resist to BMSCs **(15).** There is growing evidence that multiple myeloma patients with relapsed and refractory disease do not response to thalidomide and other novel agents, including bortezomib. PACAP might enhance sensitivity or overcome resistance to novel chemotherapeutic agents, thereby improving patient outcome in multiple myeloma **(22).**

As they observed, no cytotoxicity in PBMCs freshly obtained from bone marrow aspirates at PACAP concentrations of 10^{-15} to 10^{-5} mol/L. PACAP showed potential selective cytotoxicity against the tumor cells and a clinically useful therapeutic index for PACAP in vivo **(15).**

Previous studies denoted that dexamethasone synergized with PACAP-induced cytotoxicity, suggesting differential apoptotic signaling cascades for PACAP versus dexamethasone. Dexamethasone induces caspase-9 activation via a cytochrome c–independent, second mitochondria-derived activator of caspases–dependent pathway. It's probable that low concentrations of PACAP sensitize multiple myeloma cell lines and patient cells to DNA-damaging chemotherapeutic agents **(23).**

5. PACAP and MM Bony Lesion:

PACAP can inhibit the expression of MIP-1α already at the mRNA level, suggesting that PACAP may play an important protective role in the development of MM-induced osteolysis **(24).**

II. Role of PACAP on the kidney

The Pituitary adenylate cyclase-activating polypeptide (PACAP) markedly suppresses the release of proinflammatory cytokines from light chain-stimulated human renal proximal tubule epithelial cells and prevents the resulting tubule cell injury **(15).**

Chronic renal failure is often associated with human multiple myeloma and myeloma kidney, caused by the pathogenic effects of the overproduction of κ or λ light chain immunoglobulin proteins by cancerous plasma cells **(25).**

A study showed that PACAP dramatically prevented renal proximal tubule epithelial cell injury caused by myeloma light chains both in vitro and in vivo by suppressing light chain stimulated phosphorylation of p38 mitogen-activated protein kinase (MAPK) and nuclear translocation of the p50 subunit NF-κβ. Thus, reversal of the injury may improve renal function and survival **(16).**

The beneficial effects of PACAP on renal function in MM patients and its successful use as an antitumor agent have been demonstrated in several vivo and in vitro studies. It has been described to be protective in proximal tubule cells and to affect signaling pathways involved in osteolysis or osteolytic processes **(26).**

In Vitro:

In investigation of the effectiveness of PACAP against myeloma kidney injury in vitro. Cultured proximal tubular epithelial cells were exposed to kappa light chains isolated from the urine of a patient suffering from multiple myeloma. PACAP38 could decrease the kappa light chain-induced proximal tubule epithelial cell injury and elevated expression of IL-6 and TNF-alpha PACAP receptor antagonists were used in order to clarify the receptor activation in the background of PACAP's effect. Both PAC1 and VPAC1 receptor antagonists were able to attenuate the suppressive effect of PACAP on TNF-alpha production indicating that both receptor types are involved. PACAP was proven to act through influencing p38 mitogen-activated protein kinase (MAPK) activation **(27).**

***In Vivo:**

The above-described in vitro protective effects of PACAP against myeloma light chain protein could be confirmed in vivo **(15, 16, 26).** Rats were treated with myeloma light chain and received intravenous PACAP injections, which abolished the increase in TNF-alpha. Interestingly, despite the general protective effects of PACAP, myeloma cell proliferation was suppressed both directly and indirectly through interleukin-6 suppression. Inhibition of growth in myeloma cells through IL-6 suppression is mediated through the human PAC1 receptor short subtype and/or VPAC2 receptor **(15, 28).** In a single patient case study, PACAP was confirmed to act against myeloma kidney injury **(16)**. A decrease in lambda light chains in the urine was measured through the 24-h observation period, in spite of unchanged another laboratory parameter **(28).**

Similarly to dexamethasone, PACAP also inhibits the growth of plasma cells. As it regulates the production of several proinflammatory mediators (e.g., TNF-α, IL-6, MIP-1α) and may affect the complex cytokine network of the bone marrow microenvironment, which is altered by the MM cells **(29).**

The expression of PAC1 receptor mRNA has been detected in human bone marrow stromal cells, MM cells, and proximal tubule cells **(20).** The antitumor activity of the peptide has been described in MM, and PACAP has also been shown to be protective in the development of osteolytic bone destruction and disease-related renal injury **(26).**

PACAP may play a key role by reducing oxidative stress, preventing DNA damage, and the development of structural and numerical chromosomal aberrations characteristic of the disease **(30).**

Apoptosis and cell cycle dysregulation are also pathogenic factors in MM, which could be affected by PACAP through the regulation of cyclin D1, Ki67, and various anti-apoptotic proteins (e.g., Bcl-2). Previous research suggests that PACAP restores cell cycle control in MM and, like dexamethasone, can induce apoptosis in MM cells. It has also been described that PACAP sensitizes MM cells to DNA-damaging therapeutic agents, and when used in combination with dexamethasone, it has a synergistic effect by enhancing caspase-9 activation via cytochrome c **(27).** PACAP could also affect the activation of MYC via the PI3K-mTOR pathway and the function of DNA repair systems by affecting cyclin D **(20).**

III. Therapeutic and prognostic roles of PACAP in MM

In a clinical trial, Li and colleagues administered PACAP-38 as a continuous infusion to an 81-year-old patient with active MM. The results were encouraging, as the patient's free lambda light chain excretion was reduced after starting therapy. The literature suggests that antiproliferative effects on plasma cells (subsequent reduction in light chain production) and both direct (via PAC1 receptor) and indirect (cytokine-mediated antioxidant function) effects on tubule cells may play an important role in mitigating MM related renal dysfunction **(16).**

It is also known that PACAP may play an important role in hematopoiesis and in the development of cells from the mesodermal maturation lineage. Peptide promotes the hematopoietic stem cell population via the PAC1 receptor by increasing the number of cells in the S phase of the cell cycle by enhancing the mRNA expression of cyclin D1 and Ki67 proteins **(20).**

Furthermore, PAC1 receptor expression is higher on CD34+ stem cells and decreases or disappears with cell maturation. It is suggested that PACAP detectable in the bone marrow is of neuronal origin, and sympathetic innervation may be responsible for PACAP-regulated hematopoiesis in the bone marrow **(20).**

This is also suggested by our finding that PACAP increased with the deepening of therapeutic response, and with a reduction in the disease burden until the mean and median values of MRD negative reached those of the healthy age- and gender matched control group. We cannot exclude the possibility that these two factors occur together. We believe that the decrease in PACAP levels with age favors the development of the disease, during which plasma cells have an adverse impact on the micro-environment, causing a subsequent drop in peptide levels and a corresponding decline in tumor control. In addition to these factors, decreased PACAP level also influences the development and progression of disease-related organ damage such as renal failure and bone lesions, as a result of the peptide's antiproliferative action as well as the protective effect in proximal tubule cells and the inhibitory effect on osteoclasts **(26, 27)**

PACAP is also closely related to disease burden, as results indicate that patients with active disease, higher plasma cell infiltration in bone marrow, higher tumor markers (LDH, B2M, BJ protein), and higher ISS stage have lower PACAP levels. However, these results do not imply that peptide directly and exclusively affects the number of plasma cells. This is also supported by the fact that although most of our NDMM patients had a similar disease burden, those with higher PACAP levels achieved a deeper response and prolonged survival. Examining the PFS of our patients who achieved complete remission or MRD negative, we also found a significant positive correlation with the PACAP levels. We suggest that the plasma PACAP level could reflect not only the disease burden, but also the extent of the inflammatory changes in the bone marrow microenvironment that persist after hematological remission and may promote disease recurrence **(31).**

The prognostic role of PACAP is clearly evident, and in the future, it may also provide a new dimension to the diagnostic process (e.g., non-secretory MM). Since it is known that the synthesis of various microenvironmental proteins changes in MGUS, SMM, and MM, it is reasonable to assume that PACAP levels may vary over the course of progression from premalignant states to symptomatic disease, and that this peptide may represent an early predictor of disease progression. Unquestionably, this assumption of ours requires further investigation and expansion of the study group to include individuals suffering from these premalignant diseases **(2).**

These factors suggest an antitumor and renoprotective effect of PACAP in MM and open the possibility of using this peptide in clinical practice. The changes in the PACAP-38 levels in patients with MM were assessed to explore the role of this peptide as a potential biomarker in this disease. The detectable changes in the PACAP- 38 levels were correlated with other markers used in clinical practice to gain an understanding of the pathogenic role of this peptide **(2).**

References:

1. Xu, L., & Wu, S. (2023). New diagnostic strategy for multiple myeloma: A review. *Medicine (Baltimore), 102*(52), e36660. https://doi.org/10.1097/MD.0000000000036660

2. Tóth, D. (2023). Role of endocrine PACAP in age-related diseases. Frontiers in Endocrinology. https://doi.org/10.3389/fendo.2023.1118927
3. Tóth, D., Alizadeh, H., Polgár, B., et al. (2023). Diagnostic and prognostic value of PACAP in multiple myeloma. International Journal of Molecular Sciences, 24(13), 10801. https://doi.org/10.3390/ijms241310801
4. Wu, R., Cao, C.-X., Cao, L., Su, J., Liao, K.-M., Li, H., … Chen, J.-Y. (2024). PACAP38 synergizes with irradiation to suppress the proliferation of multiple cancer cells via regulating SOX6/Wnt/β-catenin signaling. Frontiers in Pharmacology, 15, 1492453. https://doi.org/10.3389/fphar.2024.1492453
5. International Myeloma Working Group. (2003a). Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: A report of the International Myeloma Working Group. British Journal of Haematology, 121(5), 749–757.
6. Rajkumar, S. V. (2016). Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management. American Journal of Hematology, 91(7), 719–734.
7. Soliman, A.M.; Das, S.; Teoh, S.L.(2021). Next-Generation Biomarkers in Multiple Myeloma: Understanding the Molecular Basis for Potential Use in Diagnosis and Prognosis. *Int. J. Mol. Sci.* , *22*, 7470.
8. Fotiou D, Katodritou E.(2025). From Biology to Clinical Practice: The Bone Marrow Microenvironment in Multiple Myeloma. J Clin Med. Jan 8;14(2):327.https://doi.org/10.3390/jcm14020327
9. Pham, D.; Polgar, B.; Toth, T.; Jungling, A.; Kovacs, N.; Balas, I.; Pal, E.; Szabo, D.; Fulop, B.D.; Reglodi, D.; et al.(2022). Examination of pituitary adenylate cyclase-activating polypeptide in Parkinson's disease focusing on correlations with motor symptoms. *Geroscience* , *44*, 785–803.
10. Hideshima T, Bergsagel PL, Kuehl WM, Anderson KC.(2004). Advances in biology of multiple myeloma: clinical applications. Blood ;104:607–18.
11. Hideshima T, Nakamura N, Chauhan D, AndersonKC.(2001). Biologic sequelae of interleukin-6 induced PI3-K/Akt signaling in multiple myeloma. Oncogene ;20:5991–6000.
12. Podar K, Tai YT, Davies FE, et al.(2001). Vascular endothelialgrowth factor triggers signaling cascades mediatingmultiple myeloma cell growth and migration. Blood ;98:428–35.
13. Hideshima T, Anderson KC.(2002). Molecular mechanismsof novel therapeutic approaches for multiple myeloma.Nat Rev Cancer ;2:927–37.
14. Roato I, Grano M, Brunetti G, et al.(2005). Mechanisms ofspontaneous osteoclastogenesis in cancer with bone involvement. FASEB J ;19:228–30.
15. Li, M.; Cortez, S.; Nakamachi, T.; Batuman, V.; Arimura, A. (2006).Pituitary adenylate cyclase-activating polypeptide is a potent inhibitor of the growth of light chain-secreting human multiple myeloma cells. *Cancer Res.* , *66*, 8796–8803.
16. Li, M.; Maderdrut, J.L.; Lertora, J.J.; Batuman, V.(2007). Intravenous infusion of pituitary adenylate cyclase-activating polypeptide (PACAP) in a patient with multiple myeloma and myeloma kidney: A case study. *Peptides* , *28*, 1891–1895
17. Ashina, H., Christensen, R.H., Hay, D.L. et al.(2024) Pituitary adenylate cyclase-activating polypeptide signalling as a therapeutic target in migraine. Nat Rev Neurol 20, 660–670 .
18. Damiano JS, Dalton WS.(2000). Integrin-mediated drug resistance in multiple myeloma. Leuk Lymphoma ; 38:71–81.
19. Moody TW, Ito T, Osefo N, Jensen RT (2011) VIP and PACAP: recent insights into their functions/roles in physiology and disease from molecular and genetic studies. Curr Opin Endocrinol Diabetes Obes 18:61–67.
20. Xu, Z.; Ohtaki, H.; Watanabe, J.; Miyamoto, K.; Murai, N.; Sasaki, S.; Matsumoto, M.; Hashimoto, H.; Hiraizumi, Y.; Numazawa, S.; et al.(2016). Pituitary adenylate cyclase-activating polypeptide (PACAP) contributes to the proliferation of hematopoietic progenitor cells in murine bone marrow via PACAP-specific receptor. *Sci. Rep.* , *6*, 22373.
21. Yang, W., and Lin, S. (2015). Mechanisms of drug resistance in relapse and refractory multiple myeloma. BioMed Res. Int. 2015, 341430.

22. Ludwig H, Adam Z, Hajek R, et al.(2010). Light chain-induced acute renal failure can be reversed by bortezomib-doxorubicin-dexamethasone in multiple myeloma: results of a phase II study. J Clin Oncol ;28:4635-41.
23. Chauhan D, Hideshima T, Rosen S, Reed JC,Kharbanda S, Anderson KC. (2001). Apaf-1/cytochrome c -independent and Smac-dependent induction of apoptosisin multiple myeloma (MM) cells. J Biol Chem ;276:24453–6.
24. Pozo, D.; Guerrero, J.M.; Calvo, J.R. (2002). Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit LPS-stimulated MIP-1alpha production and mRNA expression. *Cytokine* , *18*, 35–42.
25. Kundu S, Jha S B, Rivera A P, et al. (February 25, 2022) Multiple Myeloma and Renal Failure: Mechanisms, Diagnosis, and Management. Cureus 14(2): e22585.
26. Li, M.; Maderdrut, J.L.; Lertora, J.J.; Arimura, A.; Batuman, V. (2008).Renoprotection by pituitary adenylate cyclase-activating polypeptide in multiple myeloma and other kidney diseases. *Regul. Pept.* , *145*, 24–32.
27. Arimura, A.; Li, M.; Batuman, V.(2006) Potential protective action of pituitary adenylate cyclase-activating polypeptide (PACAP38) on in vitro and in vivo models of myeloma kidney injury. *Blood* , *107*, 661–668.
28. Horvath, G.; Reglodi, D.; Czetany, P.; Illes, A.; Reman, G.; Fekete, A.; Toth, G.; Laszlo, E.; Opper, B.(2019). Effects of pituitary adenylate cyclase activating polypeptide in human proximal tubule cells against gentamicin toxicity. *Int. J. Pept. Res. Ther.* , *25*, 257–264.
29. Tlili, M , Rouatbi, S , Sriha, B , Ben Rhouma, K , Sakly, M , Vaudry, D , Wurtz, O , Tebourbi, O.(2015). Pituitary Adenylate Cyclase-Activating Polypeptide Reverses Ammonium Metavanadate-Induced Airway Hyperresponsiveness in Rats. Oxid. Med. Cell.Longev. , 2015, 787561.
30. Huang, J.; Waters, K.A.; Machaalani, R.(2017).Hypoxia and nicotine effects on pituitary adenylate cyclase activating polypeptide(PACAP) and its receptor 1 (PAC1) in the developing piglet brainstem. Neurotoxicology , 62, 30–38.
31. de Jong, M.M.E.; Kellermayer, Z.; Papazian, N.; Tahri, S.; Hofste Op Bruinink, D.; Hoogenboezem, R.; Sanders, M.A.; van de Woestijne, P.C.; Bos, P.K.; Khandanpour, C.; et al.(2021). The multiple myeloma microenvironment is defined by an inflammatory stromal cell landscape. *Nat. Immunol.* , *22*, 769–780.