



Hypothesis

Macrophages and Urokinase Plasminogen Activator Receptor System in Multiple Myeloma: Case Series and Literature Review

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Abstract: The microenvironment plays an essential role in multiple myeloma (MM) development, progression, cell proliferation, survival, immunological escape, and drug resistance. Mesenchymal stromal cells and macrophages release tolerogenic cytokines and favor anti-apoptotic signaling pathway activation, while the urokinase plasminogen activator receptor (uPAR) system contributes to migration through an extracellular matrix. Here, we first summarized the role of macrophages and the uPAR system in MM pathogenesis, and then we reported the potential therapeutic effects of uPAR inhibitors in a case series of primary MM-derived adherent cells. Our preliminary results showed that after uPAR inhibitor treatments, interleukin-6 (mean \pm SD, 8734.95 \pm 4169.2 pg/mL vs. 359.26 \pm 393.8 pg/mL, pre- vs. post-treatment; $p = 0.0012$) and DKK-1 levels (mean \pm SD, 7005.41 \pm 6393.4 pg/mL vs. 61.74 \pm 55.2 pg/mL, pre- vs. post-treatment; $p = 0.0043$) in culture medium were almost completely abolished, supporting further investigation of uPAR blockade as a therapeutic strategy for MM treatment. Therefore, uPAR inhibitors could exert both anti-inflammatory and pro-immunosurveillance activity. However, our preliminary results need further validation in additional in vitro and in vivo studies.

Keywords: macrophages; urokinase plasminogen activator receptor; multiple myeloma



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1. Introduction

Multiple myeloma (MM), a malignant hematological disorder characterized by the clonal expansion of malignant plasma cells in the BM, is still considered an incurable disease because of the high incidence of relapse/refractoriness even to novel targeted therapies [1]. In MM, malignant cell growth and survival strongly rely on microenvironment stimuli, as neoplastic plasma cells are unlikely to survive outside the bone marrow (BM) [2–6], and complex cross-talks between stromal cells and neoplastic clones might favor the transition from premalignant conditions to active MM [6–9]. The microenvironment plays an important role in modulating immune surveillance against tumor cells and in facilitating tumor growth and angiogenesis [10]. Within the BM microenvironment in MM, mesenchymal stem cells (MSCs) and macrophages are essential for plasma cell proliferation, angiogenesis, immunotolerance, and drug resistance [11–15]. Indeed, CD68⁺ and CD163⁺ MM-associated macrophages at diagnosis are proposed as prognostic factors [16,17].

Macrophages, phagocytic cells, play an important role in innate immune responses with pleiotropic actions [4] and are divided into two phenotypically and functionally different subpopulations: anti-inflammatory M1 and pro-inflammatory M2 cells [18]. Classically activated M1 macrophages are antigen-presenting cells, have phagocytic activity, are positive for CD80, CD86, CD16, and CD32, and their polarization is induced by proinflammatory T helper (Th)1 cytokines (e.g., interferon[IFN]- γ) [4,18]. Conversely, M2 macrophages have anti-inflammatory properties, appear later for the resolution of inflammation, are induced by Th2 cytokines (mainly IL-4 and IL-13), and are positive for CD206 [4,9,18–20]. Impaired M1–M2 switch during inflammation or altered polarization can promote cancer initiation and progression [4].

In newly diagnosed MM, the BM is populated by CD68⁺CD163⁺ macrophages that support the survival, proliferation, and drug resistance of MM cells [7,9,12,16,17]. Circulating monocytes accumulate in the BM because neoplastic plasma cells produce monocyte-attracting chemokines, such as chemokine ligand 2 (CCL2), and release soluble cleaved uPAR (c-suPAR) [6,11,12,21,22]. Once in the BM, macrophages initially polarize toward the M1 phenotype and start sustaining the neoangiogenesis, immune escape, and drug resistance of neoplastic plasma cells [12,23–25]. Subsequently, M2 macrophages support the survival and proliferation of MM cells through the autocrine secretion of IL-6 [7,24–26]. Indeed, increased BM frequency of M2 macrophages is associated with poor prognosis and advanced disease, while no expansion is observed in premalignant conditions [7,16,19,27–30]. Moreover, M2 macrophages accumulate in the necrotic center of plasmacytomas where neoangiogenesis and tissue remodeling are required for tumor growth, while pro-inflammatory M1 macrophages are distributed in the invasive border to continuously recruit immune cells [12]. M2-polarized macrophages are also unable to phagocyte or direct the adaptive response toward neoplastic plasma cells, likely because of the CD47 inhibitory signal of macrophage phagocytosis by MM cells [12,31]. In *in vitro* co-culture systems with MSCs and MM cells, macrophages demonstrate an increased expression of several cytokines and vascular endothelial growth factors, favoring MM cell proliferation and neoangiogenesis [4,7,9,12,14,32,33]. MM-associated macrophages also release urokinase-type plasminogen activator (uPA), matrix metalloproteinases (MMPs), and macrophage-colony stimulating factor (M-CSF) that contribute to osteoclast differentiation and bone remodeling [34]. Furthermore, in *in vitro* co-culture systems with macrophages, MM cells acquire resistance to various anti-myeloma agents, such as melphalan and bortezomib [4,35]. Indeed, macrophages prevent drug-induced apoptosis by reducing caspase-3 cleavage through selectin glycoprotein ligand 1 (PSGL-1) and intercellular adhesion molecule-1 (ICAM-1) on MM cells and E/*p* selectins and CD18 on macrophages [12,36].

uPAR, a glycosyl-phosphatidylinositol (GPI)-anchored surface receptor, binds its ligand uPA and localizes its proteolytic activity on cell membranes [37,38]. In physiological conditions, uPA and uPAR are expressed by leukocytes, endothelial cells, and fibroblasts, and regulate cell adhesion and migration [39–41]. Plasmin-mediated matrix proteolysis induces the release of several growth factors via the extracellular matrix, such as VEGF [42]. uPAR also regulates cell adhesion through full-length uPAR-integrin binding, especially fibronectin $\alpha 3\beta 1$ - $\alpha 5\beta 1$ receptors and macrophage 1 antigen (Mac-1) [43]. Monocytes express uPAR, especially at the migration front providing directionality and circumscription to proteolytic matrix remodeling [44,45]. Monocyte chemotaxis is also guided by N-formylated Met-Leu-Phe (fMLF) peptides recognized by fMLF receptors FPR1, FPR2, and FPR3 [46,47]. Once uPAR is cleaved, an SRSRY sequence is exposed and can bind and activate FPR2, acting as a potent chemoattractant [46]. uPAR also influences monocyte-to-macrophage differentiation through Mac-1 (CD11b/CD18) signaling, while PAI-1 inhibits both differentiation and adhesion [48–50]. Moreover, Mac-1 interacts with uPAR during phagocytosis, leading to RAC-1 activation, a key regulator of phagocytosis [51]. Moreover, uPAR⁺ tumor cells could modulate macrophage polarization toward the M2 phenotype through TGF- β signaling pathways after uPA-uPAR cleavage-dependent activation [19,52,53], while TGF- β induces uPA expression on cancer cells in positive feedback [52–56]. Therefore, targeting

uPAR could prevent monocyte recruitment and reduce malignant plasma cell survival, diffusion, and osteolytic lesions; however, blocking it may affect macrophage recruitment, adhesion, differentiation, phagocytosis, and polarization. The prevention of uPA binding to its uPAR receptor only results in modest effects on tumor progression and metastatic invasion [57]. Therefore, novel therapies are targeting other uPAR ligands, including integrins and vitronectin [57,58].

2. Preliminary Study: Potential Clinical Relevance of uPAR Blockade in MM

In this work, we reported potential therapeutic strategies to target macrophages and microenvironments by testing several uPAR inhibitors in a case series of MM-derived adherent primary cell lines. First, adherent cells from healthy and MM subjects were characterized by morphology and flow cytometry immunophenotyping. At light microscopy examination, adherent cells had fibroblast-like spindle shapes; however, diffuse monocyte-like cells were also observed (Figure 1).

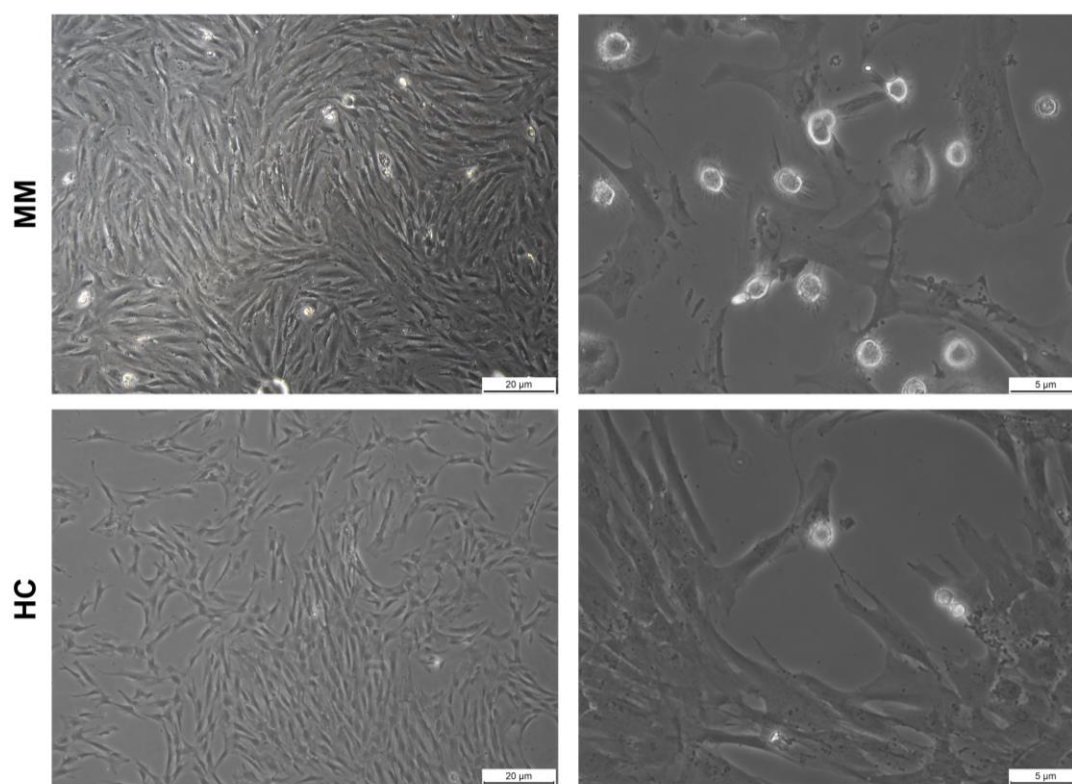


Figure 1. Brightfield images of adherent cells. Images were captured using a Leica DMIL LED microscope and acquired by Leica DFC425 C Camera after 14 days of culture of multiple myeloma (MM)-derived adherent cells (**upper panels**) or healthy-control (HC)-derived cells (**bottom panels**).

The presence of these two different populations was also confirmed by flow cytometry immunophenotyping showing a mesenchymal-like population with positivity for CD90 and negativity for CD14, CD45, and HLA-DR [59,60], while a small fraction (0.2–2.6% of total nucleated cells) had an M2-macrophage-like phenotype with positivity for CD163 and CD206 (Figure 2).

IL-1, TNF- α , IL-15, IL-10, MIP-1 α , and 1 β were not measurable at baseline or after treatment. Conversely, IL-6 (mean \pm SD, 7897.99 \pm 4255.5 pg/mL vs. 962.2 \pm 1462.5 pg/mL, MM vs. controls; $p = 0.0013$ by uncorrected Fisher's LSD test) and DKK-1 (mean \pm SD, 6516.44 \pm 5842.6 pg/mL vs. 1041.1 \pm 652.1 pg/mL, MM vs. controls; $p = 0.0073$ by uncorrected Fisher's LSD test) were significantly increased in the media MM patients after 21 days of culture compared to healthy controls (Figure 3). HGF was slightly increased in MM,

although not significantly (mean \pm SD, 987.16 ± 1323.2 pg/mL vs. 109.1 ± 57.2 pg/mL, MM vs. controls; $p = 0.6258$ by uncorrected Fisher's LSD test).

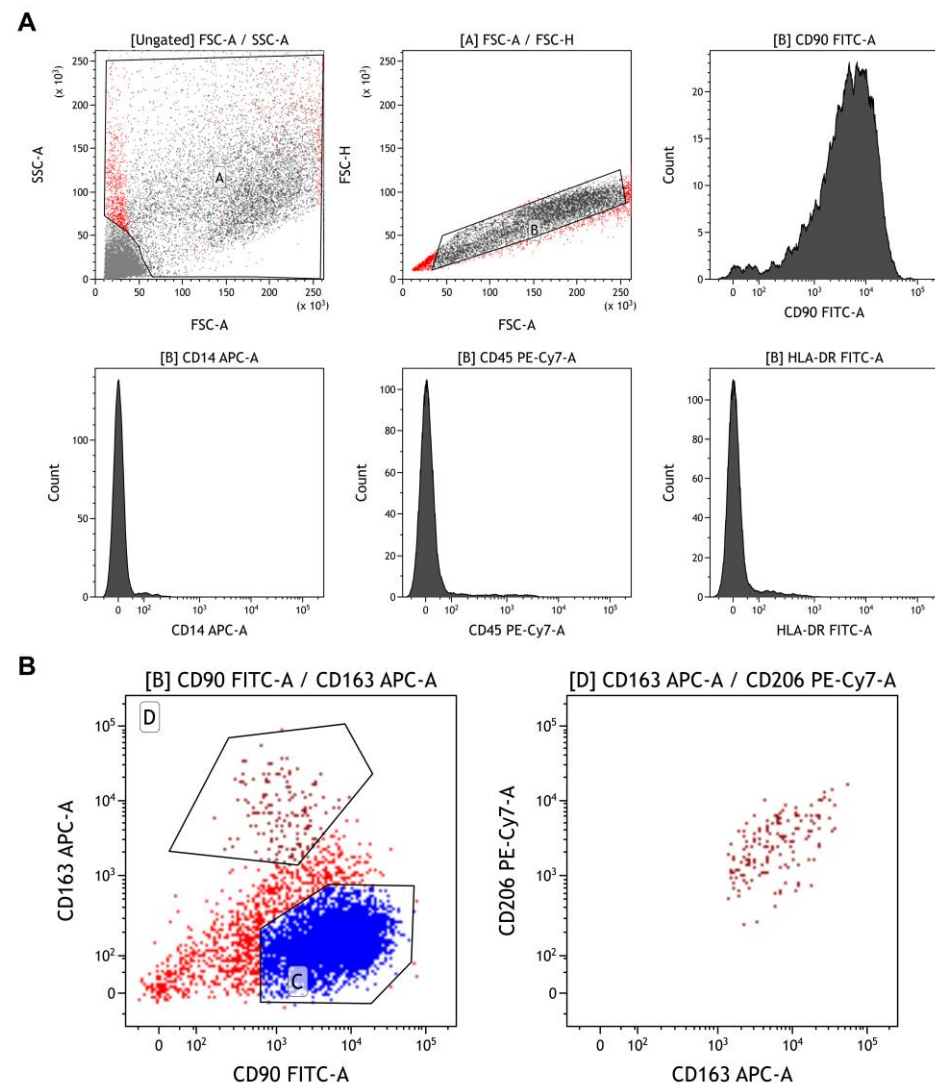


Figure 2. Immunophenotyping of adherent MM-derived cells. (A) Expression of CD90 (a mesenchymal marker), CD14, CD45, and HLA-DR was investigated on single cells gated first on linear parameters (FSC-A vs. SSC-A; gate A), and then by removing double cells (FSC-A vs. FSC-H; gate B). (B) Non-mesenchymal CD90⁺ cells were gated for CD163 expression (gate D) and further investigated for CD206. Mesenchymal CD90⁺ cells (gate C) were also identified.

Next, MM-derived mesenchymal cells were treated with C6 or C37 for 1 h, and cytokine levels were measured in culture media (Figure 4). All four compounds induced a significant decrease in IL-6 and DKK-1 levels (all $p < 0.05$ by uncorrected Fisher's LSD test), more markedly after C6 treatment. Indeed, IL-6 levels significantly decreased to 522.6 ± 265.9 pg/mL with C37, and to 79.25 ± 10.4 pg/mL with C6. Similarly, DKK-1 significantly decreased to 60.95 ± 86.2 pg/mL with C37, and to 6.95 ± 9.8 pg/mL with C6.

After C6 treatment, IL-6 (mean \pm SD, 8018.35 ± 4121.5 pg/mL vs. 324.59 ± 362.4 pg/mL, pre- vs. post-treatment; $p = 0.0003$) and DKK-1 levels (mean \pm SD, 7199.65 ± 5738.2 pg/mL vs. 56.1 ± 51.3 pg/mL, pre- vs. post-treatment; $p = 0.0007$) were almost completely abolished (Figure 5).

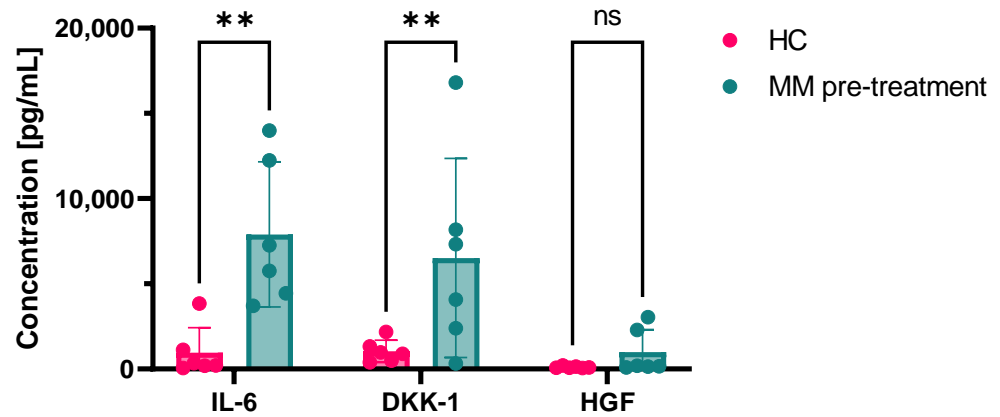


Figure 3. Cytokine production at baseline. Levels of interleukin-6 (IL-6), Dickkopf-related protein 1 (DKK1), and hepatocyte growth factor (HGF) in culture media were measured at baseline in healthy controls (HC) and multiple myeloma (MM) patients after 21 days of culture. ** $p < 0.01$; ns, not statistically significant.

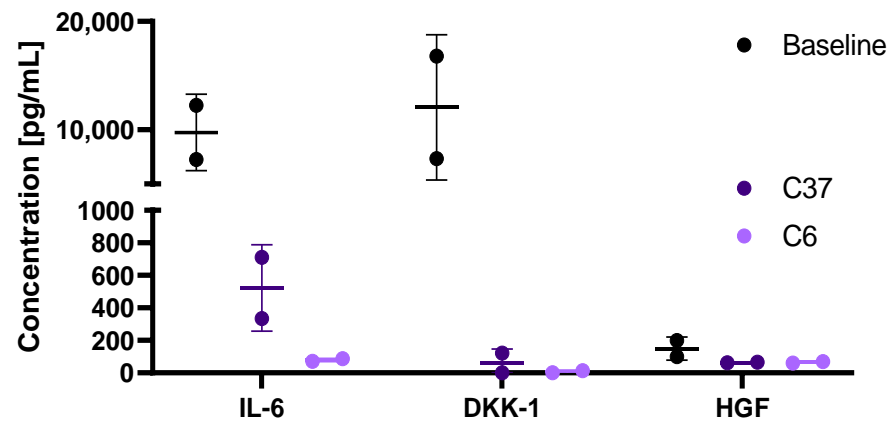


Figure 4. Cytokine levels after uPAR inhibitor treatment. Levels of interleukin-6 (IL-6), Dickkopf-related protein 1 (DKK1), and hepatocyte growth factor (HGF) in culture media were measured at baseline of multiple myeloma (MM) patients after 21 days of culture, and after treatment with uPAR inhibitors, C37 and C6.

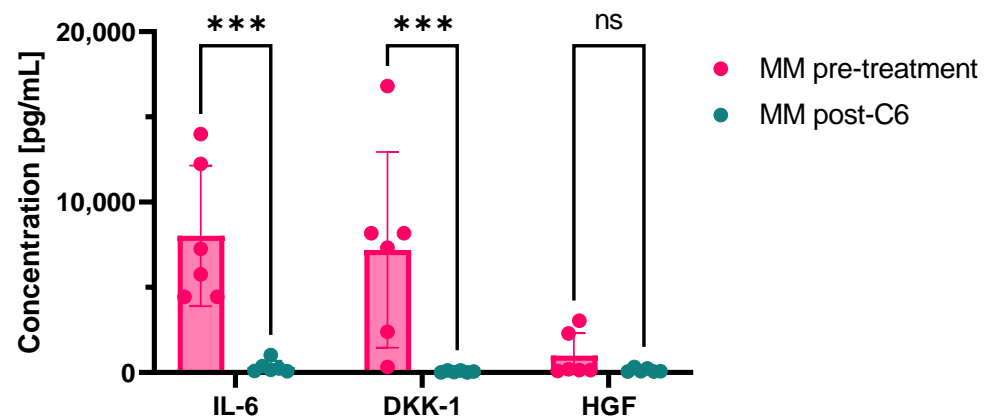


Figure 5. Cytokine levels after C6 treatment. Levels of interleukin-6 (IL-6), Dickkopf-related protein 1 (DKK1), and hepatocyte growth factor (HGF) in culture media were measured at baseline of multiple myeloma (MM) patients after 21 days of culture and after treatment with C6. *** $p < 0.001$; ns, not statistically significant.

3. Discussion

In MM, uPAR has been proposed as a prognostic marker of disease progression, as its levels correlate with tumor burden and increased uPAR⁺ plasma cells can identify MM progression early on [22,39,61]. Immature CD45⁺ MM cells show higher uPAR levels compared to mature CD45⁻/^{dim} plasma cells [62]; however, the exact mechanisms triggered by the uPA-uPAR system for promoting MM cell proliferation are still unclear. In a preliminary study, we tested two uPAR inhibitors, C6, and C37, identified by the structure-based virtual screening of the National Cancer Institute (National Cancer Institute, National Health Institutes, Bethesda, MD, USA) in primary MM cells [63]. These molecules have shown selective activities in cell adhesion to vitronectin inhibition and in uPAR interaction with the fMLF family of chemotaxis receptors (fMLF-Rs) [63]. C37 is also under investigation for the development of novel antifibrotic therapies, because of its ability to reduce oxidative stress in dermal fibroblasts isolated from the skin of patients with systemic sclerosis [64]. These compounds have demonstrated great ability in vitro to reduce extracellular matrix invasion, thus representing new promising therapeutic targets. In this work, we reported the potential therapeutic effects of C6 and C37 uPAR inhibitors in a case series of MM-derived adherent primary cell lines.

Neoplastic plasma cells produce HGF that is cleaved and activated by uPA and plasmin, leading to IL-11 secretion by osteoblasts and tumor cell invasion mediated by osteoclasts, as uPA inhibition also halts MM invasion [39,65,66]. MM plasma cells also interact with vitronectin and fibronectin through an $\alpha 5 \beta 3$ integrin and adhere to the extracellular matrix, increasing cell proliferation and MMPs and uPA secretion [67]. However, our preliminary data showed that no significant variations were observed in the culture media of MM primary cell lines at baseline and after uPAR inhibitor treatments, suggesting that HGF-related pathways are not activated outside the BM niche without extracellular matrix interaction.

MM-associated macrophages actively contribute to immunosuppression, disease progression, and drug resistance; therefore, this cell population is emerging as a potential therapeutic target [9,31,68,69]. Numerous strategies have been evaluated to promote the anti-tumor potential of macrophages, such as the use of JAK1/2 inhibitor, ruxolitinib, to reverse M2 polarization in favor of the M1 phenotype in vitro and in vivo MM models [30]. Moreover, macrophage genetic reprogramming can be performed at the epigenetic level using histone deacetylase inhibitors (HDACi), TLRs agonists, or cytokine modulators, such as with a combination of GM-CSF (a pro-M1 molecule) and 4-iodo-6-phenyl-pyrimidine (an inhibitor of a pro-M2 cytokine, MIF) [31,70,71]. Our data show stronger anti-inflammatory and pro-immunosurveillance activities in MM primary cells of C6 compared to C37, likely because of its structure and binding modes to uPAR. In particular, C6 mimics vitronectin residues responsible for insertion into uPAR's surface, making H-bonding and hydrophobic interactions; at the same time, C6 interacts with R91 and S88, two key residues of the SRSRY sequence, that could interfere with uPAR/fMLF-R crosstalk. Conversely, C37 only partially contacts this sequence [63].

The microenvironment plays an essential role in cancer development and progression, as also described in MM. Indeed, MM cell proliferation, survival, immunological escape, and drug resistance are deeply influenced by tumor-associated cell populations, including mesenchymal stromal cells and macrophages [72]. These cells alter the tumor microenvironment with the release of tolerogenic cytokines, while also favoring anti-apoptotic signaling pathway activation and drug resistance by cell-to-cell contacts with neoplastic clones. The uPA/uPAR system plays an important role in cancer development and progression, especially in favoring migration through the extracellular matrix; however, several other mechanisms might be involved in MM progression, thus proposing the uPA/uPAR system as a candidate therapeutic target [63,64,73]. Our preliminary results showed that uPAR inhibition exerted a potent anti-inflammatory effect by almost abolishing IL-6 and DKK-1 secretion; in particular, DKK-1 glycoprotein, an inhibitory component of the Wnt pathway, promotes pathological type 2 cell-mediated inflammation and immune evasion

and induces immunosuppressive macrophages in several cancers [74,75]. In MM, DKK-1 is highly expressed by myeloma cells and regulates myeloma bone disease, defined as the displacement of hematopoiesis and the formation of osteolytic lesions via osteoblast inhibition and osteoclast activation [76]. Moreover, DKK-1 is highly secreted in bortezomib-resistant MM by sustaining drug resistance through CD138 downregulation and CKAP4 receptor-mediated NF- κ B activation [77]. In addition, IL-6 contributes to DKK-1-mediated drug resistance, as this cytokine stimulates CKAP4 expression [77]. Therefore, the simultaneous abolishment of IL-6 and DKK-1 by C6 and C37 uPAR inhibitors in our encouraging preliminary results proposes these molecules as promising targeted therapy in MM and opens new perspectives on the pathogenic role of uPAR in MM and drug resistance, as uPAR inhibitors could exert both anti-inflammatory and pro-immunosurveillance activity. However, our preliminary results need further validation in additional *in vitro* and *in vivo* studies.

4. Materials and Methods

4.1. BM-MSC Culture Conditions

To preliminarily investigate the potential anti-cancer effects of C6 and C37 in MM, six MM patients (M/F, 4/2; mean age, 59 years old; range, 43–68 years) were included in this study, and BM specimens were collected in ethylenediaminetetraacetic acid (EDTA) tubes at diagnosis according to the Declaration of Helsinki and protocols approved by the local ethic committee (Campania Sud; prot./SCCE n. 24988). BM was obtained from four healthy controls (M/F, 3/1; mean age, 39 years old; range, 22–55 years old). Briefly, total BM aspirate was seeded at a concentration of 50,000 total nucleated cells/cm² in T75 plastic flasks in minimum essential medium alpha (α -MEM) supplemented with 1% GlutaGroTM (Corning, Manassas, VA, USA), 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin (Pen/Strep), and were incubated at 37 °C, 5% CO₂, and 95% relative humidity, as previously described [78,79]. After 72 h, nonadherent cells were removed, while adherent cells were kept in culture until day 21. Once cell cultures reached 70–80% confluence, cells were detached using 0.05% trypsin-0.53 mM EDTA and washed with 1 \times of phosphate-buffered saline (PBS) (Corning Cellgro, Manassas, VA, USA).

The mesenchymal phenotype was confirmed according to the International Society of Cellular Therapy guidelines: (i) the ability to adhere to tissue culture plastics; (ii) a fibroblast-like spindle shape; and (iii) a characteristic immunophenotype by flow cytometry [59].

4.2. Flow Cytometry

For immunophenotyping, a minimum of 1 \times 10⁵ cells were stained with the following antibodies: 2.5 μ L of fluorescein isothiocyanate (FITC)-conjugated anti-CD90 or 5 μ L of FITC-conjugated anti-HLA-DR; 5 μ L of allophycocyanin (APC)-conjugated anti-CD14 or CD163; and 10 μ L of phycoerythrin cyanin 7 (PC7)-conjugated anti-CD45 or anti-CD206 (all antibodies from Beckman Coulter, Fullerton, CA, United States). Cells were incubated at room temperature (RT) for 20 min in the dark, washed with phosphate-buffered saline (PBS, GibcoTM, Grand Island, NY, USA), and resuspended in 300 μ L of the same buffer for acquisition, performed on a BD FACSVerser flow cytometer (Becton Dickinson, Franklin Lakes, NJ, USA) equipped with blue (488 nm) and red lasers (628 nm). PMT voltage setting and compensation were carried out using single-color controls for each fluorochrome and an unstained sample as a negative control. All samples were run with the same PMT voltages, and a minimum of 30,000 events were recorded. Kaluza software (v.2.1, Beckman Coulter) was used for post-acquisition compensation and analysis, as previously described [78,79]. Cells were first identified using linear parameters (forward scatter area (FSC-A) vs. side scatter area (SSC-A)), and double cells were excluded (area vs. height, FSC-A vs. FSC-H) (Figure 2A). On single cells, CD90, CD45, CD14, and HLA-DR expression was investigated, while on CD163⁺CD90⁻ cells, CD206 expression was further studied (Figure 2B).

4.3. Anti-uPAR Treatment and Cytokine Detection

Next, a minimum of 4×10^3 cells were treated with C6 or C37 at a final concentration of 50 μ M for 1 h at 37 °C, 5% CO₂, and 95% relative humidity. The culture medium was collected on day 21 and after uPAR inhibitor treatment. For cytokine detection in culture medium, a bead-based multiplex custom immunoassay (9-plex LEGENDplex™ Custom Panel; BioLegend, San Diego, CA, USA) was used for the measurement of IL-1, IL-6, TNF- α , HGF, IL-15, IL-10, macrophage inflammatory protein (MIP)-1 α and 1 β , and Dickkopf-related protein 1 (DKK1). Samples were diluted 1:50 with fresh complete α -MEM and processed according to the manufacturers' instructions. Samples were run in duplicate, and cytokine quantification was performed by converting median fluorescence intensity to concentrations using a calibration made with standards as per the manufacturer's instructions. A total of 2400 total beads (1200 Beads A and 1200 Beads B) was recorded using a BD FACSVerser cytometer (BD Biosciences, Franklin Lakes, NJ, USA), and post-acquisition analysis was carried out using LEGENDplex™ Data Analysis Software Suite (BioLegend, San Diego, CA, USA).

4.4. Statistical Analysis

Data were collected in a spreadsheet and analyzed using Prism (v.9.5.1; GraphPad software, San Diego, CA, USA). A two-group comparison was carried out via an unpaired t-test, while a multiple-group comparison was carried out via ANOVA with an uncorrected Fisher's LSD test. A *p* value < 0.05 was considered statistically significant.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are available upon request by the authors.

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

References

1. De Novellis, D.; Fontana, R.; Giudice, V.; Serio, B.; Selli, C. Innovative Anti-CD38 and Anti-BCMA Targeted Therapies in Multiple Myeloma: Mechanisms of Action and Resistance. *Int. J. Mol. Sci.* **2022**, *24*, 645. [[CrossRef](#)] [[PubMed](#)]
2. Rajkumar, S.V. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. *Am. J. Hematol.* **2022**, *97*, 1086–1107. [[CrossRef](#)]
3. Dalton, W.S. The tumor microenvironment: Focus on myeloma. *Cancer Treat. Rev.* **2003**, *29*, 11–19. [[CrossRef](#)] [[PubMed](#)]
4. Kim, J.; Denu, R.A.; Dollar, B.A.; Escalante, L.E.; Kuether, J.P.; Callander, N.S.; Asimakopoulos, F.; Hematti, P. Macrophages and mesenchymal stromal cells support survival and proliferation of multiple myeloma cells. *Br. J. Haematol.* **2012**, *158*, 336–346. [[CrossRef](#)] [[PubMed](#)]
5. Peng, K.W.; Dogan, A.; Vrana, J.; Liu, C.; Ong, H.T.; Kumar, S.; Dispenzieri, A.; Dietz, A.B.; Russell, S.J. Tumor-associated macrophages infiltrate plasmacytomas and can serve as cell carriers for oncolytic measles virotherapy of disseminated myeloma. *Am. J. Hematol.* **2009**, *84*, 401–407. [[CrossRef](#)]

6. Asimakopoulos, F.; Hope, C.; Johnson, M.G.; Pagenkopf, A.; Gromek, K.; Nagel, B. Extracellular matrix and the myeloid-in-myeloma compartment: Balancing tolerogenic and immunogenic inflammation in the myeloma niche. *J. Leukoc. Biol.* **2017**, *102*, 265–275. [[CrossRef](#)] [[PubMed](#)]
7. Beider, K.; Bitner, H.; Leiba, M.; Gutwein, O.; Koren-Michowitz, M.; Ostrovsky, O.; Abraham, M.; Wald, H.; Galun, E.; Peled, A.; et al. Multiple myeloma cells recruit tumor-supportive macrophages through the CXCR4/CXCL12 axis and promote their polarization toward the M2 phenotype. *Oncotarget* **2014**, *5*, 11283–11296. [[CrossRef](#)]
8. Danziger, S.A.; McConnell, M.; Gockley, J.; Young, M.H.; Rosenthal, A.; Schmitz, F.; Reiss, D.J.; Farmer, P.; Alapat, D.V.; Singh, A.; et al. Bone marrow microenvironments that contribute to patient outcomes in newly diagnosed multiple myeloma: A cohort study of patients in the Total Therapy clinical trials. *PLoS Med.* **2020**, *17*, e1003323. [[CrossRef](#)]
9. Sun, J.; Park, C.; Guenther, N.; Gurley, S.; Zhang, L.; Lubben, B.; Adebayo, O.; Bash, H.; Chen, Y.; Maksimos, M.; et al. Tumor-associated macrophages in multiple myeloma: Advances in biology and therapy. *J. Immunother. Cancer* **2022**, *10*, e003975. [[CrossRef](#)]
10. Bissell, M.J.; Hines, W.C. Why don't we get more cancer? A proposed role of the microenvironment in restraining cancer progression. *Nat. Med.* **2011**, *17*, 320–329. [[CrossRef](#)]
11. Berardi, S.; Ria, R.; Reale, A.; De Luisi, A.; Catacchio, I.; Moschetta, M.; Vacca, A. Multiple myeloma macrophages: Pivotal players in the tumor microenvironment. *J. Oncol.* **2013**, *2013*, 183602. [[CrossRef](#)]
12. Asimakopoulos, F.; Kim, J.; Denu, R.A.; Hope, C.; Jensen, J.L.; Ollar, S.J.; Hebron, E.; Flanagan, C.; Callander, N.; Hematti, P. Macrophages in multiple myeloma: Emerging concepts and therapeutic implications. *Leuk. Lymphoma* **2013**, *54*, 2112–2121. [[CrossRef](#)]
13. Franco, O.E.; Shaw, A.K.; Strand, D.W.; Hayward, S.W. Cancer associated fibroblasts in cancer pathogenesis. *Semin. Cell Dev. Biol.* **2010**, *21*, 33–39. [[CrossRef](#)] [[PubMed](#)]
14. Ribatti, D.; Nico, B.; Vacca, A. Importance of the bone marrow microenvironment in inducing the angiogenic response in multiple myeloma. *Oncogene* **2006**, *25*, 4257–4266. [[CrossRef](#)]
15. Xie, Y.; Yang, H.; Yang, C.; He, L.; Zhang, X.; Peng, L.; Zhu, H.; Gao, L. Role and Mechanisms of Tumor-Associated Macrophages in Hematological Malignancies. *Front. Oncol.* **2022**, *12*, 933666. [[CrossRef](#)] [[PubMed](#)]
16. Suyani, E.; Sucak, G.T.; Akyürek, N.; Sahin, S.; Baysal, N.A.; Yağcı, M.; Haznedar, R. Tumor-associated macrophages as a prognostic parameter in multiple myeloma. *Ann. Hematol.* **2013**, *92*, 669–677. [[CrossRef](#)] [[PubMed](#)]
17. Wang, H.; Hu, W.M.; Xia, Z.J.; Liang, Y.; Lu, Y.; Lin, S.X.; Tang, H. High numbers of CD163+ tumor-associated macrophages correlate with poor prognosis in multiple myeloma patients receiving bortezomib-based regimens. *J. Cancer* **2019**, *10*, 3239–3245. [[CrossRef](#)]
18. Scala, P.; Rehak, L.; Giudice, V.; Ciaglia, E.; Puca, A.A.; Selleri, C.; Della Porta, G.; Maffulli, N. Stem Cell and Macrophage Roles in Skeletal Muscle Regenerative Medicine. *Int. J. Mol. Sci.* **2021**, *22*, 10867. [[CrossRef](#)]
19. Lindsten, T.; Hedbrant, A.; Ramberg, A.; Wijkander, J.; Solterbeck, A.; Eriksson, M.; Delbro, D.; Erlandsson, A. Effect of macrophages on breast cancer cell proliferation, and on expression of hormone receptors, uPAR and HER-2. *Int. J. Oncol.* **2017**, *51*, 104–114. [[CrossRef](#)]
20. Raggi, F.; Pelassa, S.; Pierobon, D.; Penco, F.; Gattorno, M.; Novelli, F.; Eva, A.; Varesio, L.; Giovarelli, M.; Bosco, M.C. Regulation of Human Macrophage M1-M2 Polarization Balance by Hypoxia and the Triggering Receptor Expressed on Myeloid Cells-1. *Front. Immunol.* **2017**, *8*, 1097. [[CrossRef](#)]
21. Li Santi, A.; Napolitano, F.; Montuori, N.; Ragno, P. The Urokinase Receptor: A Multifunctional Receptor in Cancer Cell Biology. Therapeutic Implications. *Int. J. Mol. Sci.* **2021**, *22*, 4111. [[CrossRef](#)]
22. Shen, J.; Wang, Q.; Wang, J.; Su, G.H.; Wang, J.; Guo, S.H.; Liu, Y.A.; Wu, Z.; Liu, R.F.; Li, X.; et al. Analysis of soluble urokinase plasminogen activator receptor in multiple myeloma for predicting prognosis. *Oncol Lett.* **2015**, *10*, 2403–2409. [[CrossRef](#)]
23. Karin, M.; Greten, F.R. NF-kappaB: Linking inflammation and immunity to cancer development and progression. *Nat. Rev. Immunol.* **2005**, *5*, 749–759. [[CrossRef](#)]
24. Mantovani, A.; Garlanda, C.; Allavena, P. Molecular pathways and targets in cancer-related inflammation. *Ann. Med.* **2010**, *42*, 161–170. [[CrossRef](#)]
25. Abdi, J.; Engels, F.; Garssen, J.; Redegeld, F. The role of toll-like receptor mediated signalling in the pathogenesis of multiple myeloma. *Crit. Rev. Oncol. Hematol.* **2011**, *80*, 225–240. [[CrossRef](#)]
26. Tsan, M.F.; Gao, B. Heat shock proteins and immune system. *J. Leukoc. Biol.* **2009**, *85*, 905–910. [[CrossRef](#)] [[PubMed](#)]
27. Allavena, P.; Sica, A.; Solinas, G.; Porta, C.; Mantovani, A. The inflammatory micro-environment in tumor progression: The role of tumor-associated macrophages. *Crit. Rev. Oncol. Hematol.* **2008**, *66*, 1–9. [[CrossRef](#)]
28. Sica, A.; Schioppa, T.; Mantovani, A.; Allavena, P. Tumour-associated macrophages are a distinct M2 polarised population promoting tumour progression: Potential targets of anti-cancer therapy. *Eur. J. Cancer* **2006**, *42*, 717–727. [[CrossRef](#)] [[PubMed](#)]
29. Tiainen, S.; Tumelius, R.; Rilla, K.; Hämäläinen, K.; Tammi, M.; Tammi, R.; Kosma, V.M.; Oikari, S.; Auvinen, P. High numbers of macrophages, especially M2-like (CD163-positive), correlate with hyaluronan accumulation and poor outcome in breast cancer. *Histopathology* **2015**, *66*, 873–883. [[CrossRef](#)]

30. Chen, H.; Li, M.; Sanchez, E.; Soof, C.M.; Bujarski, S.; Ng, N.; Cao, J.; Hekmati, T.; Zahab, B.; Nosrati, J.D.; et al. JAK1/2 pathway inhibition suppresses M2 polarization and overcomes resistance of myeloma to lenalidomide by reducing TRIB1, MUC1, CD44, CXCL12, and CXCR4 expression. *Br. J. Haematol.* **2020**, *188*, 283–294. [[CrossRef](#)] [[PubMed](#)]
31. Cassetta, L.; Pollard, J.W. Targeting macrophages: Therapeutic approaches in cancer. *Nat. Rev. Drug Discov.* **2018**, *17*, 887–904. [[CrossRef](#)]
32. Mayer, H.; Bertram, H.; Lindenmaier, W.; Korff, T.; Weber, H.; Weich, H. Vascular endothelial growth factor (VEGF-A) expression in human mesenchymal stem cells: Autocrine and paracrine role on osteoblastic and endothelial differentiation. *J. Cell. Biochem.* **2005**, *95*, 827–839. [[CrossRef](#)] [[PubMed](#)]
33. Scavelli, C.; Nico, B.; Cirulli, T.; Ria, R.; Di Pietro, G.; Mangieri, D.; Bacigalupo, A.; Mangialardi, G.; Coluccia, A.M.; Caravita, T.; et al. Vasculogenic mimicry by bone marrow macrophages in patients with multiple myeloma. *Oncogene* **2008**, *27*, 663–674. [[CrossRef](#)] [[PubMed](#)]
34. Gau, Y.C.; Yeh, T.J.; Hsu, C.M.; Hsiao, S.Y.; Hsiao, H.H. Pathogenesis and Treatment of Myeloma-Related Bone Disease. *Int. J. Mol. Sci.* **2022**, *23*, 3112. [[CrossRef](#)] [[PubMed](#)]
35. De Beule, N.; De Veirman, K.; Maes, K.; De Bruyne, E.; Menu, E.; Breckpot, K.; De Raeve, H.; Van Rampelbergh, R.; Van Ginderachter, J.A.; Schots, R.; et al. Tumour-associated macrophage-mediated survival of myeloma cells through STAT3 activation. *J. Pathol.* **2017**, *241*, 534–546. [[CrossRef](#)]
36. Zheng, Y.; Yang, J.; Qian, J.; Qiu, P.; Hanabuchi, S.; Lu, Y.; Wang, Z.; Liu, Z.; Li, H.; He, J.; et al. PSGL-1/selectin and ICAM-1/CD18 interactions are involved in macrophage-induced drug resistance in myeloma. *Leukemia* **2013**, *27*, 702–710. [[CrossRef](#)] [[PubMed](#)]
37. Napolitano, F.; Montuori, N. Role of Plasminogen Activation System in Platelet Pathophysiology: Emerging Concepts for Translational Applications. *Int. J. Mol. Sci.* **2022**, *23*, 6065. [[CrossRef](#)] [[PubMed](#)]
38. Ragno, P. The urokinase receptor: A ligand or a receptor? Story of a sociable molecule. *Cell. Mol. Life Sci.* **2006**, *63*, 1028–1037. [[CrossRef](#)]
39. Béné, M.C.; Castoldi, G.; Knapp, W.; Rigolin, G.M.; Escribano, L.; Lemez, P.; Ludwig, W.D.; Matutes, E.; Orfao, A.; Lanza, F.; et al. CD87 (urokinase-type plasminogen activator receptor), function and pathology in hematological disorders: A review. *Leukemia* **2004**, *18*, 394–400. [[CrossRef](#)]
40. Gadd, S.J.; Majdic, O.; Kasinrerker, W.; Stockinger, H.; Maurer, D.; Eher, R.; Knapp, W. M5, a phosphoinositol-linked human myelomonocytic activation-associated antigen. *Clin. Exp. Immunol.* **1990**, *80*, 252–256. [[CrossRef](#)]
41. Lanza, F.; Castoldi, G.L.; Castagnari, B.; Todd, R.F., 3rd; Moretti, S.; Spisani, S.; Latorraca, A.; Focarile, E.; Roberti, M.G.; Traniello, S. Expression and functional role of urokinase-type plasminogen activator receptor in normal and acute leukaemic cells. *Br. J. Haematol.* **1998**, *103*, 110–123. [[CrossRef](#)]
42. Gorrasi, A.; Petrone, A.M.; Li Santi, A.; Alfieri, M.; Montuori, N.; Ragno, P. New Pieces in the Puzzle of uPAR Role in Cell Migration Mechanisms. *Cells* **2020**, *9*, 2531. [[CrossRef](#)] [[PubMed](#)]
43. Tarui, T.; Mazar, A.P.; Cines, D.B.; Takada, Y. Urokinase-type plasminogen activator receptor (CD87) is a ligand for integrins and mediates cell-cell interaction. *J. Biol. Chem.* **2001**, *276*, 3983–3990. [[CrossRef](#)]
44. Gyetko, M.R.; Todd, R.F., 3rd; Wilkinson, C.C.; Sitrin, R.G. The urokinase receptor is required for human monocyte chemotaxis in vitro. *J. Clin. Investig.* **1994**, *93*, 1380–1387. [[CrossRef](#)]
45. Sullivan, R.; Graham, C.H. Hypoxia-driven selection of the metastatic phenotype. *Cancer Metastasis Rev.* **2007**, *26*, 319–331. [[CrossRef](#)] [[PubMed](#)]
46. Montuori, N.; Carriero, M.V.; Salzano, S.; Rossi, G.; Ragno, P. The cleavage of the urokinase receptor regulates its multiple functions. *J. Biol. Chem.* **2002**, *277*, 46932–46939. [[CrossRef](#)]
47. Resnati, M.; Pallavicini, I.; Wang, J.M.; Oppenheim, J.; Serhan, C.N.; Romano, M.; Blasi, F. The fibrinolytic receptor for urokinase activates the G protein-coupled chemotactic receptor FPRL1/LXA4R. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 1359–1364. [[CrossRef](#)] [[PubMed](#)]
48. Nusrat, A.R.; Chapman, H.A., Jr. An autocrine role for urokinase in phorbol ester-mediated differentiation of myeloid cell lines. *J. Clin. Investig.* **1991**, *87*, 1091–1097. [[CrossRef](#)]
49. Waltz, D.A.; Sailor, L.Z.; Chapman, H.A. Cytokines induce urokinase-dependent adhesion of human myeloid cells. A regulatory role for plasminogen activator inhibitors. *J. Clin. Investig.* **1993**, *91*, 1541–1552. [[CrossRef](#)]
50. Blasi, F.; Carmeliet, P. uPAR: A versatile signalling orchestrator. *Nat. Rev. Mol. Cell Biol.* **2002**, *3*, 932–943. [[CrossRef](#)]
51. Genua, M.; D'Alessio, S.; Cibella, J.; Gandelli, A.; Sala, E.; Correale, C.; Spinelli, A.; Arena, V.; Malesci, A.; Rutella, S.; et al. The urokinase plasminogen activator receptor (uPAR) controls macrophage phagocytosis in intestinal inflammation. *Gut* **2015**, *64*, 589–600. [[CrossRef](#)] [[PubMed](#)]
52. Hu, J.; Jo, M.; Eastman, B.M.; Gilder, A.S.; Bui, J.D.; Gonias, S.L. uPAR induces expression of transforming growth factor β and interleukin-4 in cancer cells to promote tumor-permissive conditioning of macrophages. *Am. J. Pathol.* **2014**, *184*, 3384–3393. [[CrossRef](#)] [[PubMed](#)]
53. Odekon, L.E.; Blasi, F.; Rifkin, D.B. Requirement for receptor-bound urokinase in plasmin-dependent cellular conversion of latent TGF- β to TGF- β . *J. Cell. Physiol.* **1994**, *158*, 398–407. [[CrossRef](#)] [[PubMed](#)]

54. Gerwin, B.I.; Keski-Oja, J.; Seddon, M.; Lechner, J.F.; Harris, C.C. TGF-beta 1 modulation of urokinase and PAI-1 expression in human bronchial epithelial cells. *Am. J. Physiol.* **1990**, *259*, L262–L269. [[CrossRef](#)]
55. Webb, D.J.; Thomas, K.S.; Gonias, S.L. Plasminogen activator inhibitor 1 functions as a urokinase response modifier at the level of cell signaling and thereby promotes MCF-7 cell growth. *J. Cell Biol.* **2001**, *152*, 741–752. [[CrossRef](#)]
56. Sroka, I.C.; Sandoval, C.P.; Chopra, H.; Gard, J.M.; Pawar, S.C.; Cress, A.E. Macrophage-dependent cleavage of the laminin receptor $\alpha 6\beta 1$ in prostate cancer. *Mol. Cancer Res.* **2011**, *9*, 1319–1328. [[CrossRef](#)]
57. Pesapane, A.; Ragno, P.; Selleri, C.; Montuori, N. Recent Advances in the Function of the 67 kDa Laminin Receptor and its Targeting for Personalized Therapy in Cancer. *Curr. Pharm. Des.* **2017**, *23*, 4745–4757. [[CrossRef](#)]
58. Mauro, C.D.; Pesapane, A.; Formisano, L.; Rosa, R.; D'Amato, V.; Ciciola, P.; Servetto, A.; Marciano, R.; Orsini, R.C.; Monteleone, F.; et al. Urokinase-type plasminogen activator receptor (uPAR) expression enhances invasion and metastasis in RAS mutated tumors. *Sci. Rep.* **2017**, *7*, 9388. [[CrossRef](#)]
59. Dominici, M.; Le Blanc, K.; Mueller, I.; Slaper-Cortenbach, I.; Marini, F.; Krause, D.; Deans, R.; Keating, A.; Prockop, D.J.; Horwitz, E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* **2006**, *8*, 315–317. [[CrossRef](#)]
60. Manzo, P.; Scala, P.; Giudice, V.; Gorrese, M.; Bertolini, A.; Morini, D.; D'Alto, F.; Pepe, R.; Pedicini, A.; Izzo, B.; et al. c-Kit M541L variant is related to ineffective hemopoiesis predisposing to clonal evolution in 3D in vitro biomimetic co-culture model of bone marrow niche. *Heliyon* **2022**, *8*, e11998. [[CrossRef](#)]
61. Shou, L.H.; Cao, D.; Dong, X.H.; Fang, Q.; Xu, B.L.; Fei, J.P. Bone Marrow Urokinase Plasminogen Activator Receptor Levels are Associated with the Progress of Multiple Myeloma. *Chin. Med. Sci. J.* **2016**, *31*, 155–160. [[CrossRef](#)]
62. Hjertner, O.; Qvigstad, G.; Hjorth-Hansen, H.; Seidel, C.; Woodliff, J.; Epstein, J.; Waage, A.; Sundan, A.; Børset, M. Expression of urokinase plasminogen activator and the urokinase plasminogen activator receptor in myeloma cells. *Br. J. Haematol.* **2000**, *109*, 815–822. [[CrossRef](#)] [[PubMed](#)]
63. Rea, V.E.; Lavecchia, A.; Di Giovanni, C.; Rossi, F.W.; Gorrasi, A.; Pesapane, A.; de Paulis, A.; Ragno, P.; Montuori, N. Discovery of new small molecules targeting the vitronectin-binding site of the urokinase receptor that block cancer cell invasion. *Mol. Cancer Ther.* **2013**, *12*, 1402–1416. [[CrossRef](#)] [[PubMed](#)]
64. Napolitano, F.; Rossi, F.W.; Pesapane, A.; Varricchio, S.; Ilardi, G.; Mascolo, M.; Staibano, S.; Lavecchia, A.; Ragno, P.; Selleri, C.; et al. N-Formyl Peptide Receptors Induce Radical Oxygen Production in Fibroblasts Derived From Systemic Sclerosis by Interacting With a Cleaved Form of Urokinase Receptor. *Front. Immunol.* **2018**, *9*, 574. [[CrossRef](#)]
65. Khan, R.; Gupta, N.; Kumar, R.; Sharma, M.; Kumar, L.; Sharma, A. Augmented expression of urokinase plasminogen activator and extracellular matrix proteins associates with multiple myeloma progression. *Clin. Exp. Metastasis* **2014**, *31*, 585–593. [[CrossRef](#)] [[PubMed](#)]
66. Hecht, M.; Heider, U.; Kaiser, M.; von Metzler, I.; Sterz, J.; Sezer, O. Osteoblasts promote migration and invasion of myeloma cells through upregulation of matrix metalloproteinases, urokinase plasminogen activator, hepatocyte growth factor and activation of p38 MAPK. *Br. J. Haematol.* **2007**, *138*, 446–458. [[CrossRef](#)]
67. Ria, R.; Vacca, A.; Ribatti, D.; Di Raimondo, F.; Merchionne, F.; Dammacco, F. Alpha(v)beta(3) integrin engagement enhances cell invasiveness in human multiple myeloma. *Haematologica* **2002**, *87*, 836–845.
68. Li, X.; Liu, R.; Su, X.; Pan, Y.; Han, X.; Shao, C.; Shi, Y. Harnessing tumor-associated macrophages as aids for cancer immunotherapy. *Mol. Cancer* **2019**, *18*, 177. [[CrossRef](#)] [[PubMed](#)]
69. Ngambenjawang, C.; Gustafson, H.H.; Pun, S.H. Progress in tumor-associated macrophage (TAM)-targeted therapeutics. *Adv. Drug Deliv. Rev.* **2017**, *114*, 206–221. [[CrossRef](#)]
70. Feng, Y.; Mu, R.; Wang, Z.; Xing, P.; Zhang, J.; Dong, L.; Wang, C. A toll-like receptor agonist mimicking microbial signal to generate tumor-suppressive macrophages. *Nat. Commun.* **2019**, *10*, 2272. [[CrossRef](#)]
71. Gutiérrez-González, A.; Martínez-Moreno, M.; Samaniego, R.; Arellano-Sánchez, N.; Salinas-Muñoz, L.; Relloso, M.; Valeri, A.; Martínez-López, J.; Corbí, Á.L.; Hidalgo, A.; et al. Evaluation of the potential therapeutic benefits of macrophage reprogramming in multiple myeloma. *Blood* **2016**, *128*, 2241–2252. [[CrossRef](#)] [[PubMed](#)]
72. Di Marzo, L.; Desantis, V.; Solimando, A.G.; Ruggieri, S.; Annesse, T.; Nico, B.; Fumarulo, R.; Vacca, A.; Frassanito, M.A. Microenvironment drug resistance in multiple myeloma: Emerging new players. *Oncotarget* **2016**, *7*, 60698–60711. [[CrossRef](#)] [[PubMed](#)]
73. Mazar, A.P.; Ahn, R.W.; O'Halloran, T.V. Development of novel therapeutics targeting the urokinase plasminogen activator receptor (uPAR) and their translation toward the clinic. *Curr. Pharm. Des.* **2011**, *17*, 1970–1978. [[CrossRef](#)] [[PubMed](#)]
74. Shi, T.; Zhang, Y.; Wang, Y.; Song, X.; Wang, H.; Zhou, X.; Liang, K.; Luo, Y.; Che, K.; Wang, X.; et al. DKK1 Promotes Tumor Immune Evasion and Impedes Anti-PD-1 Treatment by Inducing Immunosuppressive Macrophages in Gastric Cancer. *Cancer Immunol. Res.* **2022**, *10*, 1506–1524. [[CrossRef](#)] [[PubMed](#)]
75. Chae, W.J.; Ehrlich, A.K.; Chan, P.Y.; Teixeira, A.M.; Henegariu, O.; Hao, L.; Shin, J.H.; Park, J.H.; Tang, W.H.; Kim, S.T.; et al. The Wnt Antagonist Dickkopf-1 Promotes Pathological Type 2 Cell-Mediated Inflammation. *Immunity* **2016**, *44*, 246–258. [[CrossRef](#)]
76. Zhou, F.; Meng, S.; Song, H.; Claret, F.X. Dickkopf-1 is a key regulator of myeloma bone disease: Opportunities and challenges for therapeutic intervention. *Blood Rev.* **2013**, *27*, 261–267. [[CrossRef](#)]
77. Li, X.; Wang, J.; Zhu, S.; Zheng, J.; Xie, Y.; Jiang, H.; Guo, J.; Wang, Y.; Peng, Z.; Wang, M.; et al. DKK1 activates noncanonical NF- κ B signaling via IL-6-induced CKAP4 receptor in multiple myeloma. *Blood Adv.* **2021**, *5*, 3656–3667. [[CrossRef](#)]

78. Lamparelli, E.P.; Lovecchio, J.; Ciardulli, M.C.; Giudice, V.; Dale, T.P.; Selleri, C.; Forsyth, N.; Giordano, E.; Maffulli, N.; Della Porta, G. Chondrogenic Commitment of Human Bone Marrow Mesenchymal Stem Cells in a Perfused Collagen Hydrogel Functionalized with hTGF- β 1-Releasing PLGA Microcarrier. *Pharmaceutics* **2021**, *13*, 399. [[CrossRef](#)]
79. Scala, P.; Manzo, P.; Lamparelli, E.P.; Lovecchio, J.; Ciardulli, M.C.; Giudice, V.; Selleri, C.; Giordano, E.; Rehak, L.; Maffulli, N.; et al. Peripheral blood mononuclear cells contribute to myogenesis in a 3D bioengineered system of bone marrow mesenchymal stem cells and myoblasts. *Front. Bioeng. Biotechnol.* **2023**, *10*, 1075715. [[CrossRef](#)]

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