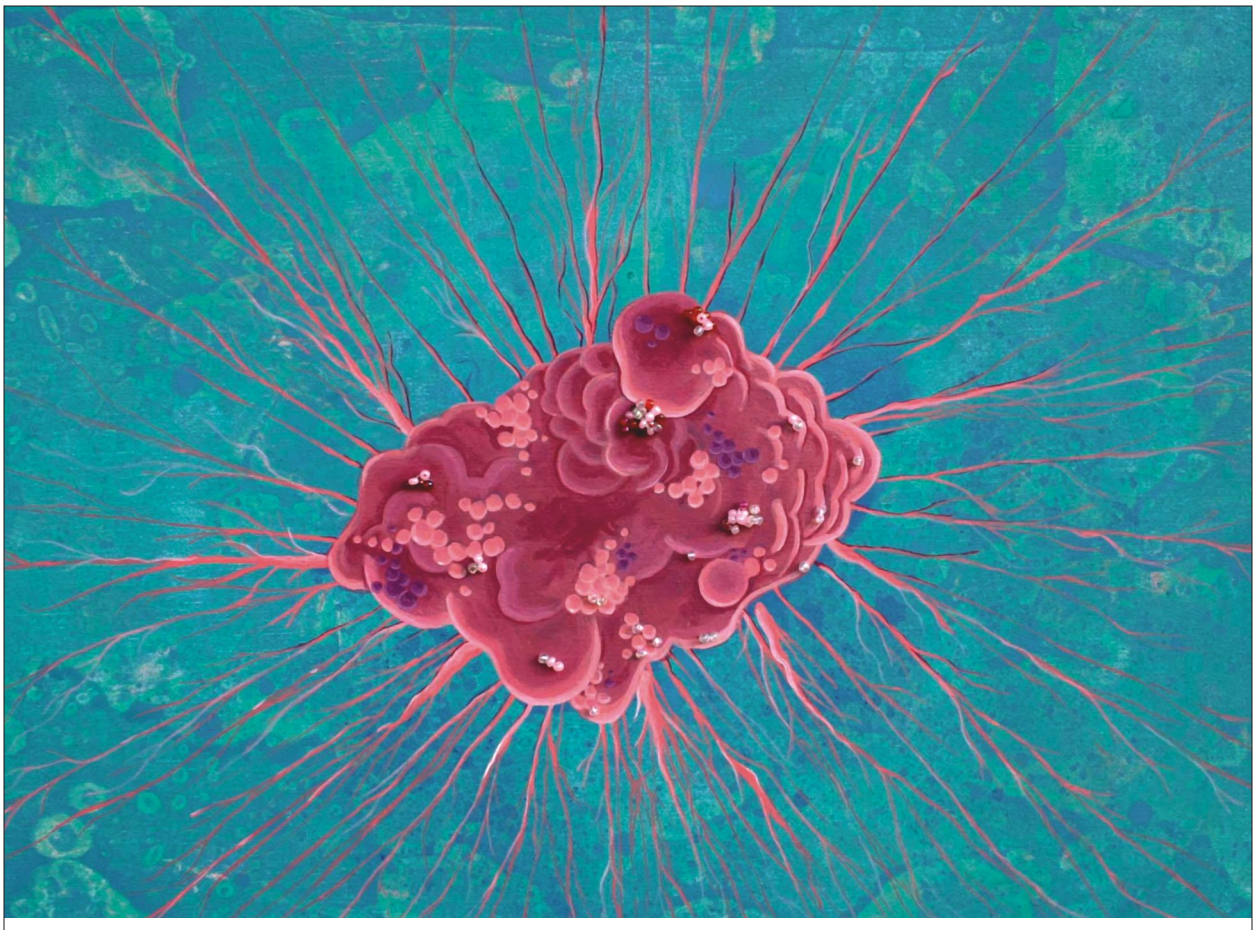

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# Research Article
# Mast Cells in Myelodysplastic Syndromes

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## Abstract

**Background and Objective:** Myelodysplastic Syndromes (MDS) are clonal haemopoietic disorders with a high frequency of leukemic transformation. The role of mast cells (MCs) in this process is not well clarified. The aim was to study the number of mast cells, the secreted cytokines and the microvascular density (MVD) in MDS and controls to clarify the possible role of mast cells in the disease progression in these patients. **Materials and Methods:** Seventy-three patients and 60 healthy individuals were involved in the study. Thirty-seven belonged to the low/intermediate-1 risk group and 36 to the high/intermediate-2 group. Toluidine blue in bone marrow smears was used for MCs measurement. Tryptase and chymase expression was estimated by immunocytochemistry. The $CD34^+$ cells were calculated by flow cytometry. Chymase and tryptase serum levels were measured by ELISA. The MVD was calculated by measuring the number of endothelial cells per 0.0625 $mm^2$ field area in paraffin sections. **Results:** An increased number of $CD34^+$ cells, as well as MCs in the bone marrow of patients, was found. The MCs in patients expressed predominantly tryptase and did not present dysplastic features. Serum tryptase was higher in MDS compared to the normals. The MVD was higher in MDS compared to normals. There was a positive correlation between $CD34^+$ cells and MCs as well as between MCs and MVD. High/intermediate-2 patients had a higher number of MCs, $CD34^+$ cells and MVD compared to low/intermediate-1 cells and normals. **Conclusion:** The MCs in MDS do not seem to belong to the malignant clone, accumulate probably reactively and may contribute to the clone evolution by supporting angiogenesis and tumour microenvironment.

Key words: Mast cells, myelodysplastic syndromes, angiogenesis, refractory anaemia, $CD34^+$ cells, tryptase, bone marrow microenvironment

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

## INTRODUCTION

Mast cells (MC) are derived from the haematopoietic progenitor cell[1] and the committed MC was isolated in 2005[2]. They contribute to tissue regeneration and tissue and organ homeostasis that present continuous increase and reconstruction through mediators they produce and store[3-17]. Their role in angiogenesis is also well-recognized[18].

In addition, MCs have a significant role in neuroimmunological regulation, neurogenesis and behaviour[15,16]. They also recognize and react to antigens, toxins and pathogens they have an antigen presentation function and they have a role in immune tolerance through a complicated network of receptors, mediators and enzymes[19-52].

In malignancies the role of MCs is controversial. In most cases increased presence of MCs is related to poor prognosis and rapid disease progression[53,54]. In some cases, MCs are related to better prognosis[55]. The MCs are attracted to the tumour environment from factors secreted by the tumour. They contribute to tumour growth through the secretion of angiogenic and mitogenic factors[56]. Their antineoplastic function is achieved through the inhibition of cell growth, induction of apoptosis, reduction of cell mobilization and enhancement of antineoplastic inflammation[57].

In haematological malignancies, MCs have been described to belong to the malignant clone or be reactive and infiltrate the microenvironment.

Myelodysplastic syndromes are a heterogeneous group of clonal hematopoietic stem cell malignancies characterized by dysplastic features, ineffective haemopoiesis and frequent evolution to acute leukaemia[58-65].

There were some publications on MCs in MDS, microvascular density (MVD) and disease progression. The results are controversial and the number of patients is small[66,67].

Hence, this article studied the number of MCs, the tryptase and chymase production and the MVD as well as their relation to the risk status of the patient to contribute to the study of the role of these cells in these syndromes.

## MATERIALS AND METHODS

**Study area:** The study was carried out at the Department of Hematology, University Hospital of Larisa, University of Thessaly, Larisa, Greece from 2009 to 2017.

**Patients:** Seventy-three consecutive patients have been studied 37 females and 36 males with MDS who were referred to the University Hospital of Larisa between the years 2009 and 2012. The median age of males was 72 years (range 35-86) and of females 69 years (range 59-81). For MDS classification $FAB_2$ and WHO 2008 classification systems were used. According to these systems, 21 patients had refractory anaemia (RA) (11 females and 10 males). The median age of males was 62 years (range 59-86) and of females 78 years (range 66-85). Eighteen patients had Refractory Anemia with Excess of Blasts (RAEB) 8 males and 10 females with the median age for males 60.5 years (range 35-75) and for females 74 years (range 58-79). Eighteen patients had Refractory Anemia with Excess of Blasts in Transformation (RAEB-T), 10 males and 8 females, with the median age for the males 66 years (range 55-77) and for the females 79.5 (range 59-80). Sixteen patients had Refractory anaemia with ringed sideroblasts (RARS) 8 males and 8 females with the median age for males 64.5 years (range 63-86) and for females 75 years (range 65-88). Patients with CMML and secondary MDS were excluded.

In addition, the patients were classified according to IPSS-1997 as low/intermediate-1 risk (37 patients) and high/intermediate-2 risk (36 patients). The median age of patients in the low/intermediate-1 risk group was 72.5 years (range 57-88) and in the high/intermediate-2 risk group was 68 years (range 35-80).

In the study, 60 normal individuals have been included 32 males and 28 females. The median age for the males was 75 years (range 56-90) and for females 74 years (range 66-90).

**Methods:** Bone marrow (BM) smears and paraffin sections were prepared from the posterior iliac crest. Mast cells were calculated using toluidine blue stain (mean value of positive cells per 1000 nucleated cells in 3 slides). For estimating the expression of tryptase and chymase mouse-anti-human moAbs were used (ABCAM -Discovery Drive, Cambridge Biomedical Campus Cambridge, CD2 OAX, UK and MA5-11717, CC1 -Thermo Fisher Scientific, Waltham, Massachusetts, USA, respectively) and PAP kit DAKO-(Agilent, Waldbronn, Germany). Every cell was graded from 0+-4+ depending on the intensity of the stain and the score was calculated as the mean value of 200 cells as Komi and Redegeld[68] described.

Haemopoietic progenitor $CD34^+$ cells were measured by flow cytometry using the anti-CD34 moAb (K567-FITC).

The levels of chymase and tryptase in serum were measured using ELISA kits (INVITROGEN-Thermo Fisher Scientific, Waltham, Massachusetts, USA) according to the manufacturer's instructions.

Microvascular density (MVD) was investigated as Kyriakou *et al.*[67] described. Microvessels were measured per 0.0625 $mm^2$ field area.

**Statistical analysis:** For statistical analysis, the t-test was used for the comparison of parametric values and Wilcoxon's test (Bonferroni's correction) for nonparametric values. The correlation coefficient ($R^2$) was used for examining possible correlations between various parameters.

## RESULTS

**$CD34^+$ cells in bone marrow:** Table 1 shows the percentage of $CD34^+$ cells in each group of patients is shown. In detail, $CD34^+$ cells in the normal individuals were 1.08±0.87%. In MDS patients they were 5.3±3.83%. Specifically, in various MDS categories, $CD34^+$ cells were 2.52±1.2% in RA, 1.37±0.5% in RARS, 8.94±2.01%in high/intermediate-2 and 2.027±1.117% in low/intermediate-1. There was a significant difference between high/intermediate-2 and normals ($p<0.01$), between high/intermediate-2 and low/intermediate-1 ($p<0.01$), between low/intermediate-1 and normals ($p<0.01$) and between RA and normals ($p<0.01$). There was no significant difference between RARS and normals ($p>0.1$).

**Mast cells in bone marrow (BMMCs):** The percentage of mast cells in bone marrow in each group of patient are shown in Table 1. In normals, the percentage of mast cells was 1.82±0.93%. In MDS it was 5.767±3.45%. In RA it was 4.38±1.16%, in RARS 2.18±0.75%, in low/intermediate-1 3.43±1.48% and in high/intermediate-2 8.16±3.26%. There was a significant difference between high/intermediate-2 and low/intermediate-1 ($p<0.01$) as well as the normals ($p<0.01$). There was a significant difference between low/intermediate and normals ($p<0.01$) as well as between RA and normals ($p<0.01$). There was no difference between RARS and normals ($p>0.1$). In the total MDS group, the mast cells were higher than the normals ($p<0.01$).

**Immunocytochemical detection of tryptase and chymase in the bone marrow:** Results are presented in Table 1. In the total MDS group, the tryptase positivity score in bone marrow mast cells (BMMC) was 2.328±1.45 while in the normals it was 0.8±0.82 and the difference was statistically significant ($p<0.01$). In high/intermediate-2 the score was 3.694±0.467 and it was significantly higher than that of low/intermediate-1 (1±0.57, $p<0.01$) and normal ($p<0.01$). In low/intermediate-1 the score did not differ from the score in normals ($p>0.1$). In MDS-RA and MDS-RARS the scores were 1.19±0.60 and 0.75±0.447, respectively and did not differ from the normals and low/intermediate-1($p>0.1$), but it was significantly lower than that of high/intermediate-2 ($p<0.01$).

The chymase score in BMMC in the total MDS group was 0.78±0.71, while in the normals it was 0.9±0.3. In high/intermediate-2 MDS the score was 0.804±0.749 and the difference between the 3 groups was not significant ($p>0.1$). In the low/intermediate-1 group the score was 0.75±0.68, in MDS-RA 0.66±0.58 and in MDS-RARS it was 0.875±0.718. There was no statistically significant difference among all groups ($p>0.1$).

**Serum tryptase and chymase levels:** The levels of serum tryptase in the normals were found 7.8±3.21 ng $mL^{-1}$, in total MDS group were 40.96±35.4, in high/intermediate-2 were 73.31±20.87, in low/intermediate-1 were 9.48±4.217, in MDS-RA 10.75±4.83, in MDS-RARS 7.806±2.503. There was a significant difference between total MDS and high/intermediate-2 compared to the low/intermediate-1 and normals ($p<0.1$). The levels of serum chymase (pg $mL^{-1}$) were not detected in any category of MDS and normals (Table 1).

**Correlation of tryptase levels and BM $CD34^+$ and mast cells:** There was a strong positive correlation between serum tryptase levels and BMMC ($R^2 = 0.6837$). There was also a positive correlation between BMMCs and BM $CD34^+$ cells ($R^2 = 0.4369$) ( Fig. 1 and 2).

**Microvascular density in bone marrow (MVD):** The MVD (microvessel number/0.0625 $mm^2$) in the entire group of MDS was 6.3±3.3 and was significantly higher than the normals (2.23±0.38, $p<0.01$). In high/intermediate-2 the MVD was 7.89±2.8, in low/intermediate-1 it was 4.8±2.2, in MDS-RA it was 4.98±1.8 and in MDS-RARS it was 5±2.0. There was a significantly higher MVD in high/intermediate-2 compared to low/intermediate-1, MDS-RA, MDS-RARS and normal ($p<0.01$). There was also a significant difference between low/intermediate-1, MDS-RA, MDS-RARS and normals ($p<0.01$). There was a positive correlation between BMMC and MVD (Fig. 3).

Table 1: Studied parameters in each group of patients and controls ($CD34^+$ cells, BMMCs, MVD, tryptase score+, chymase score and serum tryptase)

| Patients' group | $CD34^+$ cells (%) | BMMCs (%) | MVD microvessels/0.0625 $mm^2$ | Tryptase score | Chymase score | Serum tryptase (ng $mL^{-1}$) |
|---|---|---|---|---|---|---|
| MDS | 5.3±3.83 | 5.767±3.45 | 6.3±3.3 | 2.328±1.45 | 0.78±0.71 | 40.26±35.4 |
| MDS-RA | 2.52±1.2 | 4.38±1.16 | 4.98±1.8 | 1.19±0.60 | 0.66±0.58 | 10.75±4.83 |
| MDS-RARS | 1.37±0.5 | 2.18±0.75 | 5.0±2.0 | 0.75±0.447 | 0.875±0.718 | 7.806±2.503 |
| MDS low/int-1 | 2.027±1.117 | 3.43±1.48 | 4.8±2.2 | 1.0±0.57 | 0.75±0.68 | 9.48±4.217 |
| MDS high/int2 | 8.94±2.01 | 8.16±3.26 | 7.89±2.8 | 3.694±0.467 | 0.804±0.749 | 73.31±20.87 |
| Normals | 1.08±0.87 | 1.82±0.93 | 2.23±0.38 | 0.8±0.82 | 0.9±0.447 | 7.8±3.21 |

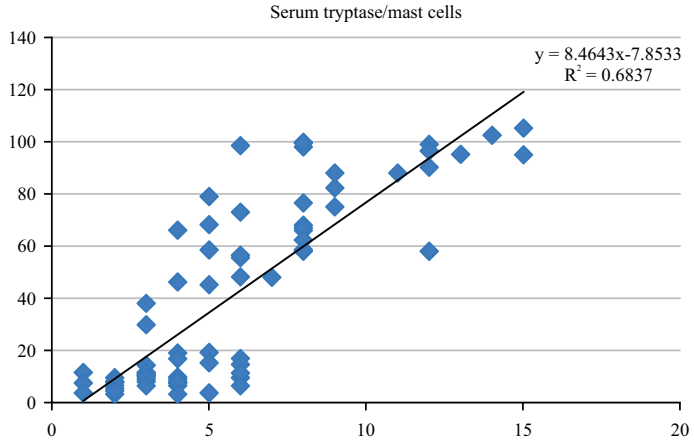


Fig. 1: Correlation between bone marrow mast cells (x-axis) and serum tryptase levels (y-axis) in MDS patients
There is a strong positive correlation between the 2 parameters ($R^2 = 0.6837$)

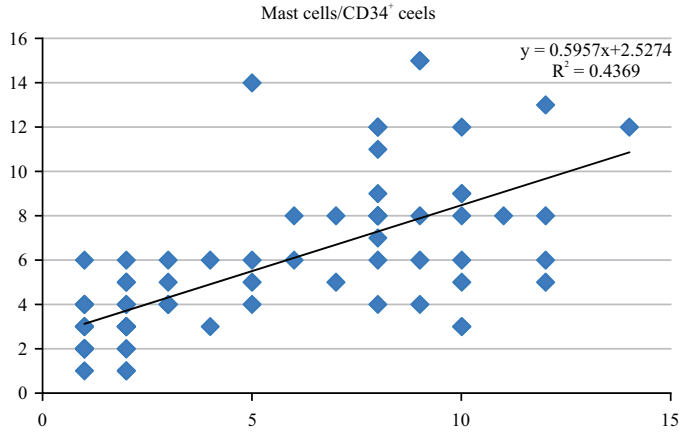


Fig. 2: Correlation between BMMCs (y-axis) and BMCD34$^+$ cells (x-axis) in MDS patients
There was a positive correlation between the 2 parameters ($R^2 = 0.4369$)

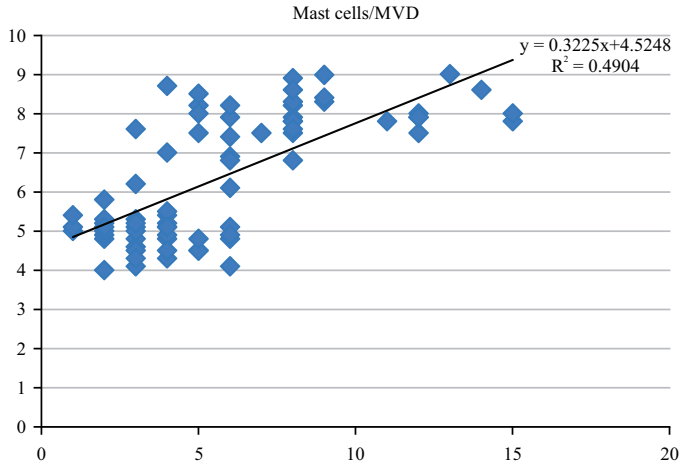


Fig. 3: Correlation between bone marrow mast cells (x-axis) and bone marrow microvessel density-MVD (y-axis) in MDS patients
There is a positive correlation between the 2 parameters ($R^2 = 0.4904$)

## DISCUSSION

An increased number of MBMCs and MVD in MDS possible pathogenetic connection between them was found in our study. There were several publications regarding the presence of mast cells in malignant diseases, including haematological malignancies and their role in disease progression is controversial. The mechanisms by which they contribute are not completely clarified[53,54,57,69,70].

A higher number of mast cells in higher-risk MDS as well as higher numbers of BMMC in the entire MDS group compared to normals was found. This was in agreement with what has been reported earlier by Alexandrakis *et al*.[66]. This also found in agreement with earlier reports by Pejler *et al*.[71] that, these cells secrete tryptase predominantly that was detected by immunocytochemistry in BM as well as in the serum of patients. In reactive mastocytosis such as in allergic conditions, it has been reported that the mast cells are tryptase and chymase-producing[72] and are peripheral and not BM mast cells. Although in a previous study there was no difference in BMMC numbers in the various MDS categories[66], an increase in BMMC in higher-risk MDS was found. The fact that was detected increased numbers of BMMC were in higher risk MDS which is considered a more advanced stage of the disease probably means that the number of BMMC increases with disease progression. Whether they contribute to the disease progression or they accumulate reactively is not clear. In earlier reports, it has been found that in some cases, the mast cells belong to the malignant clone and in these cases, they present dysplastic features[66,73,74]. In this study dysplastic features (elongated shape, abnormal granulation and abnormal accumulation) were not found in BMMC but this does not exclude the neoplastic origin of these cells. Studies during disease progression in each case, genetic studies and MC cultures could help to clarify the origin of these cells. Probably the majority of BMMCs accumulate in response to tumour-secreted factors in BM but it is not known if the cytokines that BMMCs secrete contribute to disease progression.

It has been reported that MC is involved in angiogenesis[16-18,56,57,75] and neoangiogenesis is important for tumour growth[76-78].

We found increased MVD in MDS compared to the normals. We also found higher MVD in high/intermediate-2 risk MDS compared to the low/intermediate-1, in contrast to a previous study by Kyriakou *et al*.[67]. The MVD is positively correlated with the number of BMMC. This raises the suggestion that BMMCs may contribute to tumour progression by enhancing angiogenesis. The heterogeneity of the MDS group may be responsible for the contradictive results in the literature[67].

Many previous studies suggested that MC involvement in fibrosis in many situations like liver cirrhosis, lung fibrosis, renal fibrosis, scleroderma, etc.[3,10,79]. There are no adequate data to clarify the mechanism through which MCs exert their fibrotic action. We did not have enough patients to study the possible relation of BMMCs in MDS with BM fibrosis.

## CONCLUSION

An increase in BMMCs in MDS was found and they were higher in the advanced stages of the disease. To clarify whether they contribute to disease progression further studies are required with MC cultures and clonality investigation in various stages of the disease.

## SIGNIFICANCE STATEMENT

The microenvironment plays an important role in MDS evolution. Studying the factors of the microenvironment that contribute to malignant clone growth and evolution and the use of proper agents targeting the microenvironment might help in delaying disease progression.

## REFERENCES

1. Fodinger, M., G. Fritsch, K. Winkler, W. Emminger and G. Mitterbauer *et al*., 1994. Origin of human mast cells: Development from transplanted hematopoietic stem cells after allogeneic bone marrow transplantation. Blood, 84: 2954-2959.
2. Jamur, M.C., A.C.G. Grodzki, E.H. Berenstein, M.M. Hamawy, R.P. Siraganian and C. Oliver, 2005. Identification and characterization of undifferentiated mast cells in mouse bone marrow. Blood, 105: 4282-4289.
3. Galli, S.J. and M. Tsai, 2008. Mast cells: Versatile regulators of inflammation, tissue remodeling, host defense and homeostasis. J. Dermatological Sci., 49: 7-19.
4. Jamur, M.C. and C. Oliver, 2011. Origin, maturation and recruitment of mast cell precursors. Front. Biosci., 3: 1390-1406.
5. Huang, C., G.W. Wong, N. Ghildyal, M.F. Gurish and A. Sali *et al*., 1997. The tryptase, mouse mast cell protease 7, exhibits anticoagulantactivity *in vivo* and *in vitro* due to its ability to degrade fibrinogen in the presence of the diverse array of protease inhibitors in plasma. J. Biol. Chem., 272: 31885-31893.
6. Gottwald, T., S. Coerper, M. Schäffer, G. Köveker and R.H. Stead, 1998. The mast cell-nerve axis in wound healing: A hypothesis. Wound Repair Regener., 6: 8-20.

7. Thomas, V.A., C.J. Wheeless, M.S. Stack and D.A. Johnson, 1998. Human mast cell tryptase fibrinogenolysis: Kinetics, anticoagulation mechanism, and cell adhesion disruption. Biochemistry, 37: 2291-2298.
8. Rock, M.J., J. Despot and R.F. Lemanske, 1990. Mast cell granules modulate alveolar macrophage respiratory-burst activity and eicosanoid metabolism. J. Allergy Clin. Immunol., 86: 452-461.
9. Kanwar, S. and P. Kubes, 1994. Ischemia/reperfusion-induced granulocyte influx is a multistep process mediated by mast cells. Microcirculation, 1: 175-182.
10. Levi-Schaffer, F. and A. Kupietzky, 1990. Mast cells enhance migration and proliferation of fibroblasts into an *in vitro* wound. Exp. Cell Res., 188: 42-49.
11. Katayama, I., H. Yokozeki and K. Nishioka, 1992. Mast-cell-derived mediators induce epidermal cell proliferation: Clue for lichenified skin lesion formation in atopic dermatitis. Int. Arch. Allergy Immunol., 98: 410-414.
12. Ribatti, D. and E. Crivellato, 2011. Mast Cells, Angiogenesis and Cancer. In: Mast Cell Biology, Gilfillan, A.M. and D.D. Metcalfe (Eds.), Springer, Boston, Massachusetts, ISBN: 978-1-4419-9533-9, pp: 270-288.
13. Moulin, V., G. Castilloux, F.A. Auger, D. Garrel, M.D. O'Connor-McCourt and L. Germain, 1998. Modulated response to cytokines of human wound healing myofibroblasts compared to dermal fibroblasts. Exp. Cell Res., 238: 283-293.
14. Matsuda, H., H. Koyama, H. Sato, J. Sawada and A. Itakura *et al*., 1998. Role of nerve growth factor in cutaneous wound healing: Accelerating effects in normal and healing-impaired diabetic mice. J. Exp. Med., 187: 297-306.
15. Schäffer, M., T. Beiter, H.D. Becker and T.K. Hunt, 1998. Neuropeptides: Mediators of inflammation and tissue repair? Arch. Surg., 133: 1107-1116.
16. van Nassauw, L., D. Adriaensen and J.P. Timmermans, 2007. The bidirectional communication between neurons and mast cells within the gastrointestinal tract. Auton. Neurosci.: Basic Clin., 133: 91-103.
17. Crivellato, E., C.A. Beltrami, F. Mallardi and D. Ribatti, 2004. The mast cell: An active participant or an innocent bystander? Histol. Histopathol., 19: 259-270.
18. de Palma, M., D. Biziato and T.V. Petrova, 2017. Microenvironmental regulation of tumour angiogenesis. Nat. Rev. Cancer, 17: 457-474.
19. Marshall, J.S., 2004. Mast-cell responses to pathogens. Nat. Rev. Immunol., 4: 787-799.
20. Burd, P.R., H.W. Rogers, J.R. Gordon, C.A. Martin and S. Jayaraman *et al*., 1989. Interleukin 3-dependent and -independent mast cells stimulated with IgE and antigen express multiple cytokines. J. Exp. Med., 170: 245-257.
21. Galli, S.J., J. Kalesnikoff, M.A. Grimbaldeston, A.M. Piliponsky, C.M.M. Williams and M. Tsai, 2005. Mast cells as "tunable" effector and immunoregulatory cells: Recent advances. Annu. Rev. Immunol., 23: 749-786.
22. Metcalfe, D.D., R.D. Peavy and A.M. Gilfillan, 2009. Mechanisms of mast cell signaling in anaphylaxis. J. Allergy Clin. Immunol., 124: 639-646.
23. Gilfillan, A.M. and C. Tkaczyk, 2006. Integrated signaling pathways for mast-cell activation. Nat. Rev. Immunol., 6: 218-230.
24. Galli, S.J., S. Nakae and M. Tsai, 2005. Mast cells in the development of adaptive immune responses. Nat. Immunol., 6: 135-142.
25. Wyczolkowska, J., K. Rydzynski and A. Prouvost-Danon, 1992. Concanavalin A-induced activation of hamster mast cells: Morphological changes and histamine secretion. Int. Arch. Allergy Immunol., 97: 167-172.
26. Moreno, A.N., M.C. Jamur, C. Oliver and M.C. Roque-Barreira, 2003. Mast cell degranulation induced by lectins: Effect on neutrophil recruitment. Int. Arch. Allergy Immunol., 132: 221-230.
27. de Almeida Buranello, P.A., M.R.I. Moulin, D.A. Souza Jr., M.C. Jamur, M.C. Roque-Barreira and C. Oliver, 2010. The lectin ArtinM induces recruitment of rat mast cells from the bone marrow to the peritoneal cavity. PLoS ONE, Vol. 5. 10.1371/journal.pone.0009776.
28. Hill, P.B., A.J. Macdonald, E.M. Thornton, G.F.J. Newlands, S.J. Galli and H.R.P. Miller, 1996. Stem cell factor enhances immunoglobulin E-dependent mediator release from cultured rat bone marrow-derived mast cells: Activation of previously unresponsive cells demonstrated by a novel ELISPOT assay. Immunology, 87: 326-333.
29. Hundley, T.R., A.M. Gilfillan, C. Tkaczyk, M.V. Andrade, D.D. Metcalfe and M.A. Beaven, 2004. Kit and FcεRI mediate unique and convergent signals for release of inflammatory mediators from human mast cells. Blood, 104: 2410-2417.
30. Tkaczyk, C., V. Horejsi, S. Iwaki, P. Draber and L.E. Samelson *et al*., 2004. NTAL phosphorylation is a pivotal link between the signaling cascades leading to human mast cell degranulation following Kit activation and FcεRI aggregation. Blood, 104: 207-214.
31. Metz, M., F. Siebenhaar and M. Maurer, 2008. Mast cell functions in the innate skin immune system. Immunobiology, 213: 251-260.
32. Fukuda, M., H. Ushio, J. Kawasaki, F. Niyonsaba and M. Takeuchi *et al*., 2013. Expression and functional characterization of retinoic acid-inducible gene-I-like receptors of mast cells in response to viral infection. J. Innate Immun., 5: 163-173.

33. Graham, A.C., K.M. Hilmer, J.M. Zickovich and J.J. Obar, 2013. Inflammatory response of mast cells during influenza a virus infection is mediated by active infection and RIG-I signaling. J. Immunol., 190: 4676-4684.
34. Gordon, J.R. and S.J. Galli, 1990. Mast cells as a source of both preformed and immunologically inducible TNF-α/cachectin. Nature, 346: 274-276.
35. Huang, C., D.S. Friend, W.T. Qiu, G.W. Wong, G. Morales, J. Hunt and R.L. Stevens, 1998. Induction of a selective and persistent extravasation of neutrophils into the peritoneal cavity by tryptase mouse mast cell protease 6. J. Immunol., 160: 1910-1919.
36. Biedermann, T., M. Kneilling, R. Mailhammer, K. Maier and C.A. Sander *et al*., 2000. Mast cells control neutrophil recruitment during T cell-mediated delayed-type hypersensitivity reactions through tumor necrosis factor and macrophage inflammatory protein 2. J. Exp. Med., 192: 1441-1452.
37. de Filippo, K., A. Dudeck, M. Hasenberg, E. Nye and N. van Rooijen *et al*., 2013. Mast cell and macrophage chemokines CXCL1/CXCL2 control the early stage of neutrophil recruitment during tissue inflammation. Blood, 121: 4930-4937.
38. Supajatura, V., H. Ushio, A. Nakao, K. Okumura, C. Ra and H. Ogawa, 2001. Protective roles of mast cells against enterobacterial infection are mediated by toll-like receptor 4. J. Immunol., 167: 2250-2256.
39. Rodriguez, A.R., J.J. Yu, A.K. Murthy, M.N. Guentzel and K.E. Klose *et al*., 2011. Mast cell/IL-4 control of *Francisella tularensis* replication and host cell death is associated with increased ATP production and phagosomal acidification. Mucosal Immunol., 4: 217-226.
40. Rodriguez, A.R., J.J. Yu, M.N. Guentzel, C.S. Navara and K.E. Klose *et al*., 2012. Mast cell TLR2 signaling is crucial for effective killing of *Francisella tularensis*. J. Immunol., 188: 5604-5611.
41. Feger, F., S. Varadaradjalou, Z. Gao, S.N. Abraham and M. Arock, 2002. The role of mast cells in host defense and their subversion by bacterial pathogens. Trends Immunol., 23: 151-158.
42. di Nardo, A., A. Vitiello and R.L. Gallo, 2003. Cutting edge: Mast cell antimicrobial activity is mediated by expression of cathelicidin antimicrobial peptide. J. Immunol., 170: 2274-2278.
43. Wei, O.L., A. Hilliard, D. Kalman and M. Sherman, 2005. Mast cells limit systemic bacterial dissemination but not colitis in response to *Citrobacter rodentium*. Infect. Immun., 73: 1978-1985.
44. Campagna, S., N. Saint, G. Molle and A. Aumelas, 2007. Structure and mechanism of action of the antimicrobial peptide piscidin. Biochemistry, 46: 1771-1778.
45. Malaviya, R., E.A. Ross, J.I. MacGregor, T. Ikeda, J.R. Little, B.A. Jakschik and S.N. Abraham, 1994. Mast cell phagocytosis of FimH-expressing enterobacteria. J. Immunol., 152: 1907-1914.
46. von Köckritz-Blickwede, M., O. Goldmann, P. Thulin, K. Heinemann, A. Norrby-Teglund, M. Rohde and E. Medina, 2008. Phagocytosis-independent antimicrobial activity of mast cells by means of extracellular trap formation. Blood, 111: 3070-3080.
47. Maurer, M., J. Wedemeyer, M. Metz, A.M. Piliponsky and K. Weller *et al*., 2004. Mast cells promote homeostasis by limiting endothelin-1-induced toxicity. Nature, 432: 512-516.
48. Metz, M., A.M. Piliponsky, C.C. Chen, V. Lammel and M. Åbrink *et al*., 2006. Mast cells can enhance resistance to snake and honeybee venoms. Science, 313: 526-530.
49. Schneider, L.A., S.M. Schlenner, T.B. Feyerabend, M. Wunderlin and H.R. Rodewald, 2007. Molecular mechanism of mast cell-mediated innate defense against endothelin and snake venom sarafotoxin. J. Exp. Med., 204: 2629-2639.
50. Piliponsky, A.M., C.C. Chen, T. Nishimura, M. Metz and E.J. Rios *et al*., 2008. Neurotensin increases mortality and mast cells reduce neurotensin levels in a mouse model of sepsis. Nat. Med., 14: 392-398.
51. Akahoshi, M., C.H. Song, A.M. Piliponsky, M. Metz and A. Guzzetta *et al*., 2011. Mast cell chymase reduces the toxicity of Gila monster venom, scorpion venom, and vasoactive intestinal polypeptide in mice. J. Clin. Invest., 121: 4180-4191.
52. Takanami, I., K. Takeuchi and M. Naruke, 2000. Mast cell density is associated with angiogenesis and poor prognosis in pulmonary adenocarcinoma. Cancer, 88: 2686-2692.
53. Conti, P., M.L. Castellani, D. Kempuraj, V. Salini and J. Vecchiet *et al*., 2007. Role of mast cells in tumor growth. Ann. Clin. Lab. Sci., 37: 315-322.
54. Dabiri, S., D. Huntsman, N. Makretsov, M. Cheang and B. Gilks *et al*., 2004. The presence of stromal mast cells identifies a subset of invasive breast cancers with a favorable prognosis. Mod. Pathol., 17: 690-695.
55. Ch'ng, S., R.A. Wallis, L. Yuan, P.F. Davis and S.T. Tan, 2006. Mast cells and cutaneous malignancies. Mod. Pathol., 19: 149-159.
56. Dyduch, G., K. Kaczmarczyk and K. Okon, 2012. Mast cells and cancer: Enemies or allies? Pol. J. Pathol., 63: 1-7.
57. Kurzrock, R., 2002. Myelodysplastic syndrome overview. Semin. Hematol., 39: 18-25.
58. Valent, P. and H.P. Horny, 2009. Minimal diagnostic criteria for myelodysplastic syndromes and separation from ICUS and IDUS: Update and open questions. Eur. J. Clin. Invest., 39: 548-553.
59. Warlick, E.D. and B.D. Smith, 2007. Myelodysplastic syndromes: Review of pathophysiology and current novel treatment approaches. Curr. Cancer Drug Targets, 7: 541-558.

60. Scott, B.L. and H.J. Deeg, 2010. Myelodysplastic syndromes. Annu. Rev. Med., 61: 345-358.
61. Greenberg, P.L., 1983. The smoldering myeloid leukemic states: Clinical and biologic features. Blood, 61: 1035-1044.
62. Koeffler, H.P. and D.W. Golde, 1980. Human preleukemia. Ann. Intern. Med., 93: 347-353.
63. Noël, P. and L.A. Solberg Jr., 1992. Myelodysplastic syndromes: Pathogenesis, diagnosis and treatment. Crit. Rev. Oncol. Hematol., 12: 193-215.
64. Helström-Lindberg, E., M. Tobiasson and P. Greenberg, 2020. Myelodysplastic syndromes: Moving towards personalized management. Haematologica, 105: 1765-1779.
65. Dunphy, C.H., 2005. Evaluation of mast cells in myeloproliferative disorders and myelodysplastic syndromes. Arch. Pathol. Lab. Med., 129: 219-222.
66. Alexandrakis, M.G., F.H. Passam, C.A. Pappa, J. Damilakis and G. Tsirakis *et al*., 2005. Serum evaluation of angiogenic cytokines basic fibroblast growth factor, hepatocyte growth factor and TNF-ALPHA in patients with myelodysplastic syndromes: Correlation with bone marrow microvascular density. Int. J. Immunopathol. Pharmacol., 18: 287-295.
67. Kyriakou, D., A.G. Eliopoulos, A. Papadakis, M. Alexandrakis and G.D. Eliopoulos, 1998. Decreased expression of c-*myc* oncoprotein by peripheral blood mononuclear cells in thalassaemia patients receiving desferrioxamine. Eur. J. Haematol., 60: 21-27.
68. Komi, D.E.A. and F.A. Redegeld, 2020. Role of mast cells in shaping the tumor microenvironment. Clin. Rev. Allergy Immunol., 58: 313-325.
69. Hanes, M.R., C.A. Giacomantonio and J.S. Marshall, 2021. Mast cells and skin and breast cancers: A complicated and microenvironment-dependent role. Cells, Vol. 10. 10.3390/cells10050986.
70. Horny, H.P., A. Greschniok, J.H. Jordan, D.M. Menke and P. Valent, 2003. Chymase expressing bone marrow mast cells in mastocytosis and myelodysplastic syndromes: An immunohistochemical and morphometric study. J. Clin. Pathol., 56: 103-106.
71. Pejler, G., E. Rönnberg, I. Waern and S. Wernersson, 2010. Mast cell proteases: Multifaceted regulators of inflammatory disease. Blood, 115: 4981-4990.
72. Ribatti, D., G. Polimeno, A. Vacca, A. Marzullo and E. Crivellato *et al*., 2002. Correlation of bone marrow angiogenesis and mast cells with tryptase activity in myelodysplastic syndromes. Leukemia, 16: 1680-1684.
73. Yang, L., Y. Qian, E. Eksioglu, P.K. Epling-Burnette and S. Wei, 2015. The inflammatory microenvironment in MDS. Cell. Mol. Life Sci., 72: 1959-1966.
74. D'Amore, P.A. and R.W. Thompson, 1987. Mechanisms of angiogenesis. Annu. Rev. Physiol., 49: 453-464.
75. Weidner, N., J. Folkman, F. Pozza, P. Bevilacqua and E.N. Allred *et al*., 1992. Tumor angiogenesis: A new significant and independent prognostic indicator in early-stage breast carcinoma. J. Natl. Cancer Inst., 84: 1875-1887.
76. Chung, Y.S., K. Maeda and M. Sowa, 1996. Prognostic value of angiogenesis in gastro-intestinal tumours. Eur. J. Cancer, 32: 2501-2505.
77. Aguayo, A., F.M. Armillas-Canseco and D. Martinez-Banos, 2011. Antiangiogenesis in myelodysplastic syndrome. Curr. Cancer Drug Targets, 11: 1044-1052.
78. Kong, P., P. Christia and N.G. Frangogiannis, 2014. The pathogenesis of cardiac fibrosis. Cell. Mol. Life Sci., 71: 549-574.
79. Strattan, E., S. Palaniyandi, R. Kumari, J. Du and N. Hakim *et al*., 2019. Mast cells are mediators of fibrosis and effector cell recruitment in dermal chronic graft-vs.-host disease. Front. Immunol., Vol. 10. 10.3389/fimmu.2019.02470.