

Plasma Cell Spatial Distribution Pattern Correlates with Unique Molecular Profiling Signature

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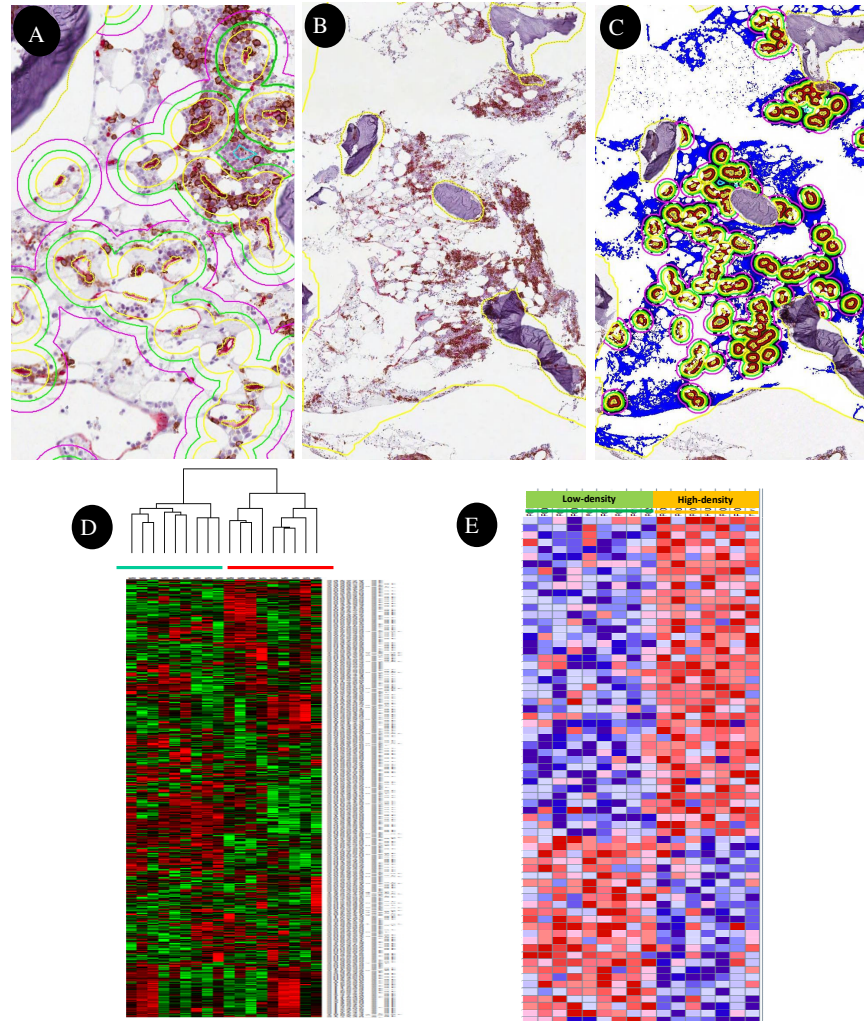
BACKGROUND

- Bone marrow (BM) angiogenesis is typically increased in multiple myeloma (MM)
- Microvessel density (MVD) is a known indicator of poor prognosis.
- The difficulty of detecting 3D vessels from 2D cut sections has previously limited the study of spatial distribution of plasma cells (PC) and their interaction with BM microenvironment.
- We utilized a novel whole tissue image (WSI) analysis approach (AngioMap) to identify vessels, then applied computational grown regions extended out from each vessel to identify the spatial distribution of PC.
- PC distribution was correlated with gene expression profile in a cohort of cases.

MATERIALS & METHODS

- Diagnostic samples from 16 patients with adequate archival pathology materials and available gene expression profiling data were included in the study.
- CD34 (Red)/CD138 (Brown) double stained (Figure A) bone marrow core biopsy slides were digitally scanned using Aperio XT Scanscope (Aperio Technologies, CA)..
- After identifying vessels and drawing regions of 15 and 35 m from vessels (Figure A), we identified both plasma and normal haematopoietic (NH) cells in these regions.
- The following statistics across the entire hematopoietic regions of the slides (excluding bone and poor histology areas) (Figures B&C) were computed using Angiomap algorithm (Flagship Biosciences Inc., Flagstaff, United States):
 - Total PC / NH count,
 - PC count within 15 & 35 m of vessels borders,
 - MVD.
- Cases were stratified based on MVD into high and low density group as well as PC/NH ratio within 15 m from vessels based on best discriminating cut-off point . .

FIGURES



MATERIALS AND METHODS

Results: AngioMap analysis of the 16 samples showed a spectrum of PC to NH at <15, 15-35 and >35 m of (0.04-84), (0.04-131.41), and (0.02-21.76), respectively. Unsupervised cluster analysis produced two major dendrogram branches (C). Supervised hierarchic clustering performed on two subgroups based on low/high MVD and low/high PC density within 15 m distance as designated by AngioMap findings identified 70 genes with differential expression between both groups based on statistically significant P value.

RESULTS

- AngioMap analysis of the 16 samples showed a spectrum of PC to NH at <15, 15-35 and >35 m of (0.04-84), (0.04-131.41), and (0.02-21.76), respectively.
- Supervised hierarchic clustering performed on the identical two subgroups based on low/high MVD and low/high PC density within 15 m distance as designated by AngioMap findings identified 70 genes with differential expression between both groups based on statistically significant P value.

CONCLUSIONS

- PC spatial distribution patterns and MVD are associated with distinct gene expression profile.
- The use of dual staining immunohistochemistry in conjunction with WSI techniques is a powerful technique for better characterization of the plasma cell in core biopsies.
- This is the first study that profiles the distribution of PC around vessels across whole sections, and has widespread applications in other areas, including stem cell biology