MCPIP1 Deficiency and Unregulated Inflammatory Disease

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Introduction
It is a well-accepted notion that the fundamental root of most of the disease processes that plague mankind are based in inflammatory changes. This is a very complex cascade of actions at the cellular level and to this day, many of these processes are still being defined. One of these very important cellular modulators of stress response has been identified to be the Monocyte Chemotactic Protein-Induced Protein 1 of the zinc finger protein family "Hypothesis
If one examines the histologic structure of mice who are MCPIP1 deficient, then one will see structural evidence of increased cellular production and decreased regulation of the bone marrow immune-products.

Methods
MCPIP1-deficient (MCPIP1−/−) mice and its wild-type (MCPIP1+/+) littermates on a C57BL/6 background were generated and maintained in sterilized filter-top cages. Diet fed consisted of autoclaved food and water under specific pathogen-free conditions. All of mice used were between the ages of 6-12 weeks except when indicated. Experimental procedures were approved by the Animal Care and Use Committee of University of Missouri Kansas City. The mice were then sacrificed and histological sections were taken of the long bones. A total of four WT slides containing a total of 23 fields and a total of 16 KO slides with a total of 134 fields underwent microscopic and results recorded. Data were calculated using STATISTICA software.

Results

Figure 1. Control spleen (left) and MCPIP1 knockout spleen (right) revealed normal bone marrow structure and function as an extension of its inflammatory regulatory processes.

Figure 2. Control lung (left) and MCPIP1 knockout lung (right) at 100x H&E stain. Control exhibits normal alveolar development of surrounding tissues at 100x H&E stain. Control shows normal structure and regulatory processes.

Figure 3. Control bone cross-section 100x (left) revealed normal bone marrow structure and relatively balanced distributions of granulocytes and megakaryocytes, per field examined. MCPIP1-knockout 100x (right) shows loss of organization and expansion of marrow.

Figure 4. Control bone cross section 400x (left) revealed maintained organization and distributions of granulocytes and megakaryocytes. MCPIP1 knockout cross section 400x (right) revealed histologically significant expansion of the bone marrow and significant hypodifferentiation of both granulocytes and megakaryocytes within the bone marrow, per field examined.

Figure 5. The basis of this study is to have shown grave systemic consequences of unregulated activity of MCPIP-1 (fig. 1 & 2). The basis of this study is to have shown grave systemic consequences of unregulated activity of MCPIP-1 (fig. 1 & 2).

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Figure 1. Control spleen (left) and MCPIP1 knockout spleen (right) revealed normal bone marrow structure and relatively balanced distributions of granulocytes and megakaryocytes, per field examined. MCPIP1-knockout 100x (right) shows loss of organization and expansion of marrow.

Figure 2. Control lung (left) and MCPIP1 knockout lung (right) at 100x H&E stain. Control exhibits normal alveolar development structure without any obvious pathology. MCPIP1-KO was notable for vast lympho-myeloid infiltration and this has been hypothesized as the probable cause of death for these subjects.

Figure 3. Control bone cross-section 100x (left) revealed normal bone marrow structure and relatively balanced distributions of granulocytes and megakaryocytes, per field examined. MCPIP1-knockout 100x (right) shows loss of organization and expansion of marrow.

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Weaknesses
Although care was taken, H&E staining and bone marrow preservation between the two models was variable in quality, making cell counts more difficult and most likely have some contribution to the broad ranges in cell counts.

Strengths and Weaknesses

Strengths: The MCPIP1-deficient (MCPIP1−/−) mice and its wild-type (MCPIP1+/+) littermates on a C57BL/6 background that were generated made great models for investigation and standardization as they did not require feedings that would interfere with bone marrow structure or production. Also, the cell counts were done by one investigator, and thus, technique was easily repeated and standard. Biostatistics were compiled and analyzed by Turkey HSD (C) and data was reviewed by multiple faculty.

Weaknesses: The molecular mechanisms underlying the pathological changes in MCPIP1-deficient mice are still not completely understood. This study, and others, have resulted suggestions that the MCPIP1 pathway to severe inflammatory disease may originate in the bone marrow. There is great interest in further evaluation of this protein as it may lead to new pharmacological targets to treat inflammatory conditions. One questioned brought about by this and related studies is where along the B-cell and neutrophil lineages does MCPIP1 exact its mechanism of inhibition? This would be best pursued by an immunohistochemical staining of the bone marrow to identify immature B-cells/neutrophils and what cellular changes are observed at each level of maturation.

Conclusion
The molecular mechanisms underlying the pathological changes in MCPIP1-deficient mice are still not completely understood. This study, and others, have resulted suggestions that the MCPIP1 pathway to severe inflammatory disease may originate in the bone marrow. There is great interest in further evaluation of this protein as it may lead to new pharmacological targets to treat inflammatory conditions. One questioned brought about by this and related studies is where along the B-cell and neutrophil lineages does MCPIP1 exact its mechanism of inhibition? This would be best pursued by an immunohistochemical staining of the bone marrow to identify immature B-cells/neutrophils and what cellular changes are observed at each level of maturation.

References
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