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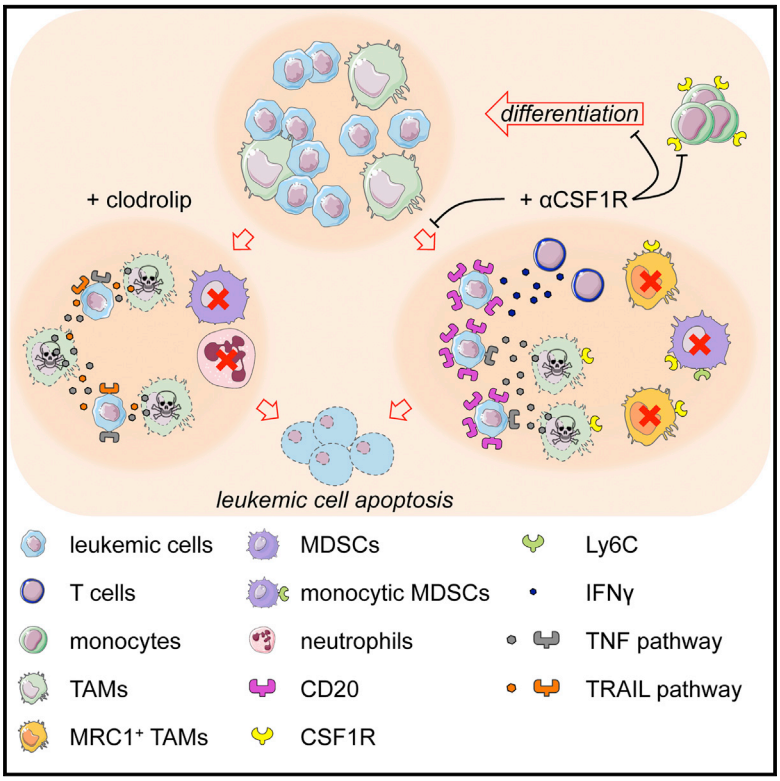
Targeting Macrophages Sensitizes Chronic Lymphocytic Leukemia to Apoptosis and Inhibits Disease Progression

Graphical Abstract



Highlights

- The macrophage transcriptome is modulated by leukemic cells
- Macrophage depletion limits survival of leukemic cells in vivo
- Macrophage killing restores apoptosis sensitivity of leukemic cells
- Macrophage targeting can be therapeutically exploited in CLL

Authors

Giovanni Galletti, Cristina Scielzo, Federica Barbaglio, ..., Michele De Palma, Federico Caligaris-Cappio, Maria Teresa Sabrina Bertilaccio

Correspondence

federico.caligaris@airc.it (F.C.-C.), bertilaccio.sabrina@hsr.it (M.T.S.B.)

In Brief

CLL is the prototype of chronic B cell tumors, and its development and progression depend on a complex network of cells including macrophages. Galletti et al. describe a set of molecular interactions supporting the in vivo dependence of leukemic cells on monocytes/macrophages and suggest therapeutic strategies based on macrophage targeting.

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Targeting Macrophages Sensitizes Chronic Lymphocytic Leukemia to Apoptosis and Inhibits Disease Progression

Giovanni Galletti,[1,2] Cristina Scielzo,[1,2] Federica Barbaglio,[1] Tania Véliz Rodriguez,[1] Michela Riba,[3] Dejan Lazarevic,[3] Davide Cittaro,[3] Giorgia Simonetti,[4] Pamela Ranghetti,[1] Lydia Scarfò,[5,6] Maurilio Ponzoni,[6,7] Martina Rocchi,[6,7] Angelo Corti,[8] Achille Anselmo,[9] Nico van Rooijen,[10] Christian Klein,[11] Carola H. Ries,[12] Paolo Ghia,[2,5,6] Michele De Palma,[13,14] Federico Caligaris-Cappio,[1,2,6,15,*] and Maria Teresa Sabrina Bertilaccio[1,2,15,*]

[1]Unit of Lymphoid Malignancies, Division of Experimental Oncology, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy
[2]Vita-Salute San Raffaele University, 20132 Milan, Italy
[3]Center for Translational Genomics and Bioinformatics, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy
[4]Department of Experimental, Diagnostic and Specialty Medicine, Institute of Hematology "L. e A. Seràgnoli," Università di Bologna, 40138 Bologna, Italy
[5]Unit of B Cell Neoplasia, Division of Experimental Oncology, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy
[6]Unit of Lymphoid Malignancies, Department of Onco-Hematology, IRCCS San Raffaele Hospital, Milan, Italy
[7]Pathology Unit, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy
[8]Tumor Biology and Vascular Targeting Unit, Division of Experimental Oncology, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy
[9]Humanitas Clinical and Research Center, 20089 Rozzano, Milan, Italy
[10]Department of Molecular Cell Biology, Vrije University Medical Center, 1081 BT Amsterdam, the Netherlands
[11]Roche Pharma Research and Early Development, Oncology Discovery, Roche Innovation Center Zurich, 8952 Zurich, Switzerland
[12]Roche Pharmaceutical Research and Early Development, Roche Innovation Center Penzberg, Oncology Discovery, 82377 Penzberg, Germany
[13]The Swiss Institute for Experimental Cancer Research (ISREC), School of Life Sciences, École Polytechnique Fédérale de Lausanne (EPFL), 1015 Lausanne, Switzerland
[14]Division of Regenerative Medicine, Stem Cells and Gene Therapy, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy
[15]Co-senior author
*Correspondence: federico.caligaris@airc.it (F.C.-C.), bertilaccio.sabrina@hsr.it (M.T.S.B.)
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SUMMARY

The role of monocytes/macrophages in the development and progression of chronic lymphocytic leukemia (CLL) is poorly understood. Transcriptomic analyses show that monocytes/macrophages and leukemic cells cross talk during CLL progression. Macrophage depletion impairs CLL engraftment, drastically reduces leukemic growth, and favorably impacts mouse survival. Targeting of macrophages by either CSF1R signaling blockade or clodrolip-mediated cell killing has marked inhibitory effects on established leukemia also. Macrophage killing induces leukemic cell death mainly via the TNF pathway and reprograms the tumor microenvironment toward an antitumoral phenotype. CSF1R inhibition reduces leukemic cell load, especially in the bone marrow, and increases circulating CD20$^+$ leukemic cells. Accordingly, co-targeting TAMs and CD20-expressing leukemic cells provides a survival benefit in the mice. These results establish the important role of macrophages in CLL and suggest therapeutic strategies based on interfering with leukemia-macrophage interactions.

INTRODUCTION

The interactive co-evolution of cancer and normal bystander cells optimizes the clonal expansion of chronic lymphoid malignancies of B cell type within specific microenvironments. Chronic lymphocytic leukemia (CLL) is the most frequent and paradigmatic chronic B cell malignancy, characterized by the growth of mature CD5$^+$ monoclonal B lymphocytes in immune-protected and protumorigenic habitats that include stromal, T, and endothelial cells (Caligaris-Cappio et al., 2014; Caligaris-Cappio and Ghia, 2008; Zenz et al., 2010). CLL cells accumulating in peripheral lymphoid organs, bone marrow (BM), and circulating in peripheral blood (PB) are the progeny of cells that proliferate in specific tissue microenvironmental niches, termed pseudofollicles (Caligaris-Cappio et al., 2014).

CLL cell cross talk with the microenvironment is largely dependent upon a functional leukemic B cell receptor (BCR). Signaling through the BCR modulates CLL cell proliferation, survival, and cytoskeletal activity and can be targeted by inhibitors that, by interfering with different BCR-associated kinases such as Bruton tyrosine kinase (BTK), also influence the interaction between CLL cells and the microenvironment (Burger and Gribben, 2014; Byrd et al., 2013). For example, the BTK inhibitor ibrutinib blocks the protective functions of stromal cells (Herman et al., 2011), which deploy signals that favor the survival of CLL cells (Lutzny et al., 2013).