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MiR-181b in B cells of chronic lymphocytic leukemia is regulated by cellular interaction with CD4⁺ T cells and increases the CTL toxicity versus the leukemic clone

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Statement of the Problem: Clinical progression of chronic lymphocytic leukemia (CLL) is characterized by immune cell dysfunction due, at least in part, to T cell defects, such as decreased expression of CD40L and reduced signaling via the TCR CD3. This compromise the ability of T cells to respond and to eliminate leukemic cell from CLL patients. Changes in microRNAs expression also characterize clinical progression of CLL with a strong decrease of miR-181b/a and miR-130a associated with the more aggressive phase of the disease. The miR-181b targets anti apoptotic proteins, such as BCL-2 and MCL1.

Aim: The purpose of this study is to find how these microRNAs are deregulated in CLL and if they are involved in the immune escape that characterize this disease.

Methodology & Findings: We co-cultured pure CLL-B cells with either activated (CD2, CD3 and CD28 antibodies, used to mimic antigen-presenting cells) or non-activated CD4⁺ T cells from healthy donors or from PBMC of CLL patients. We observed a significant increase of miR-181b and miR-130a expression in CLL B-cells after co-culture with activated CD4⁺ T cells. By the use of specific antibodies, we established that this effect is a T/B contact-dependent signaling mediated through CD40L-CD40 interaction. We determine that increased expression of the 3 miRs occurs at the transcriptional level. In this context, miR-181b enhanced the maturation and activity of cytotoxic T cells and consequently, the apoptotic response of CLL cells. This phenomenon was due, at least in part, to miR-181b-induced depletion of interleukin 10, which is a strong inhibitor of the immune response in CLL. *In vivo* experiments in NOD.Cg-Prkdc^{scid} Il2rgtm1Wjl/SzJ mice confirmed that miR-181b induces the death of CLL cells *in vivo* only when functional T cells are restored.

Conclusion & Significance: In conclusion, we demonstrate that the down-regulation of miR-181b in CLL cells is involved in the immune dysfunction that characterizes this disease. Restoration of physiological miR-181b activity in B-CLL cells may be a challenging novel approach to the treatment of CLL patients.

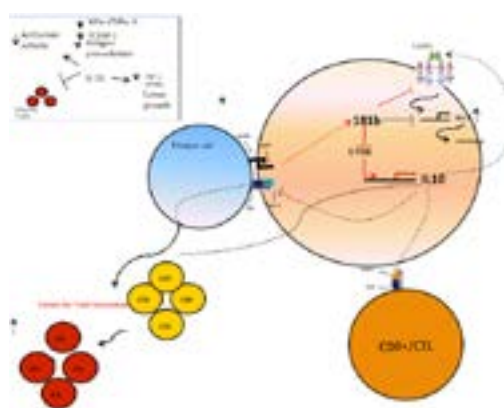


Figure 1: miR-181b potentiates T cell cytotoxic activity. Cartoon model of the miR-181b contribute in T cell-mediated immune response in CLL. In chronic B cell leukemia miR-181b is upregulated by CD40L-positive CD4⁺ T cells. In turn, miR-181b targets interleukin 10, inhibitor of the T cell cytotoxic activity. Loss of this pathway contributes to the immunodeficiency associated with progressive disease.

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Recent Publications

1. Pepe F, Pagotto S, Soliman S, Rossi C, Lanuti P, Braconi C, Mariani Costantini R, Visone R and Veronese A (2017) Regulation of miR-483-3p by the O-linked N-acetylglucosamine transferase links chemosensitivity to glucose metabolism in live cancer cells. *Oncogenesis* 6(5):e328.
2. Carotenuto P, Fassan M, Pandolfo R, Lampis A, Vicentini C, Cascione L, Paulus Hock V, Boulter L, Guest R Quagliata L, Hahne J C, Ridgway R, Jamieson T, Athineos D, Veronese A, Visone R et al. (2017) Wnt signalling modulates transcribed-ultraconserved regions in hepatobiliary cancers. *Gut* doi: 10.1136/gutjnl-2016-312278.
3. Lupini L, Pepe F, Ferracin M, Braconi C, Callegari E, Pagotto S, Spizzo R, Zagatti B, Lanuti P, Fornari F, Ghasemi R, Mariani- Costantini R, Bolondi L, Gramantieri L, Calin GA, Sabbioni S, Visone R, Veronese A and Negrini M (2016) Over-expression of the miR- 483-3p overcomes the miR 145/TP53 pro-apoptotic loop in hepatocellular carcinoma. *Oncotarget* doi:10.18632/oncotarget.8913.
4. d'Avenia M, Citro R, De Marco M, Veronese A, Rosati A, Visone R, Leptidis S, et al. (2015) A novel miR-371a-5p-mediated pathway, leading to BAG3 upregulation in cardiomyocytes in response to epinephrine, is lost in Takotsubo cardiomyopathy. *Cell Death Dis.*6:e1948.
5. Veronese A, Pepe F, Chiacchia J, Pagotto S, Lanuti P, Veschi S, Di Marco M, D'Argenio A, Innocenti I, Vannata B, Autore F, Marchisio M, Wernicke D, Verginelli F, Leone G, Rassenti L Z, Kipps T J, Mariani Costantini R, Laurenti L, Croce C M and Visone R (2014) Allele specific loss and transcription of the miR-15a/16-1 cluster in chronic lymphocytic leukemia. *Leukemia* doi: 10.1038/leu.2014.139.

Biography

Rosa Visone has her expertise in studies related to microRNAs as diagnostic, prognostic and therapeutic tools in cancer. She developed this interest during her Postdoctoral position in Dr. Croce's Laboratory. She identified microRNAs that can mark chronic lymphocytic leukemia (CLL) progression facilitating decision making for management of CLL patients. Her research also highlighted the cryptic promoter of miR-15a and miR-16-1, which seems to have a role in B-CLL cells from patients with more severe course of the leukemia.

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