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MIRNAOME DEREGULATION CAN CONTRIBUTE TO OVEREXPRESSION OF IMMUNE CHECKPOINTS: AN EPIGENETIC MECHANISM OF CHECKPOINT INHIBITOR THERAPY FAILURE

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Introduction

One of the main immune escape mechanisms used by tumors is the exploitation of immune checkpoints – receptors on surface of immune cells, which, after binding their ligands, can suppress immune response.
This research aims to identify in what way the shifts in miRNA signature can contribute to the expression of immune checkpoint ligands on cancer cells.

Reactivation of gene encoding immune checkpoint ligands

MiRNA targets within gene transcripts were predicted in silico using the TargetScan software.

Targets of miRNAs miR-15/16, miR-34, miR-140, miR-141/200, miR-145, miR-148/152, miR-199, miR-200, miR-202, miR-214, miR-302, miR-320 and miR-520 were found in *PDL1* (*CD274*) gene transcript (Fig. 1).

Down-regulation of these miRNAs is characteristic to the cancer cells and, therefore, allows reactivation and hyperexpression of gene encoding PD-1 ligand.

Moreover, multiple targets of down-regulated miRNAs let-7, miR-1/206, miR-15/16, miR-22, miR-26, miR-29, miR-31, miR-34, miR-124, miR-125, miR-128, miR-129, miR-133a/b, miR-138, miR-140, miR-141/200, miR-143, miR-145, miR-148/152, miR-149, miR-194, miR-199, miR-204, miR-205, miR-214, miR-218, miR-302, miR-326, miR-449, miR-506, miR-520 and miR-655 were revealed in transcripts of genes encoding other immune checkpoint ligands – PDL2 (PDCD1LG2), B7-H3 (CD276), B7-H4 (VTCN1), HHLA2, galectin 9 (LGALS9), HVEM, PVR (Necl-5), PVRL2 (Nectin 2) and CD200. In addition, transcript of FASL gene encoding the Fas ligand carries targets of down-regulated miRNAs let-7, miR-22, miR-141/200, miR-149, miR-194, miR-199, miR-214 and miR-302/520.

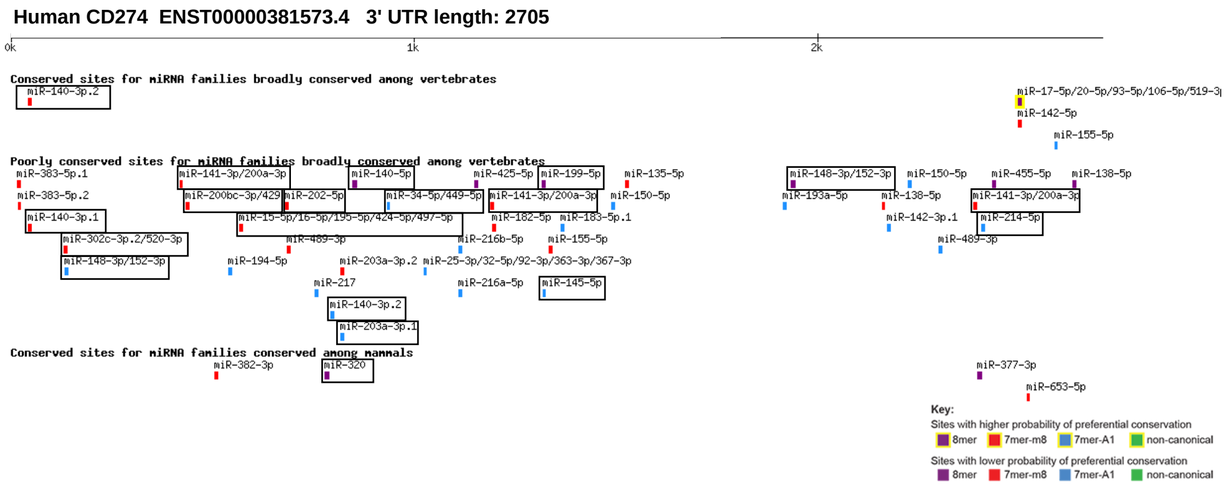

Fig. 1. miRNA binding sites in 3'-UTR regions of PDL1 (CD274) gene transcript.

Conclusions:

Down-regulation of tumor-suppressive miRNAs can be responsible for overexpression of genes encoding the key immune checkpoint ligands. As a result, cancer cells can ensure immune privilege. This resistance is multiple, because the shifts in miRNAome can cause hyperexpression of many immune checkpoint ligands at one time. Therefore, inhibition of one of the immune checkpoint axes can be easily overcome by overexpression of others due to the most profound down-regulation of the miRNA expression that is well-known phenomenon during the tumor progression and drug administration. Probably, this explains the long-term failure of immunotherapy.