Human cells may take up nucleic acids, for example ribonucleic acid (RNA) from other organisms, such as bacteria, yeast, plant cells, as well as viruses and synthetic RNA. Exogenous RNAs (exoRNAs) are involved in the regulation of host cell proliferation, differentiation and development, cell death, and immune responses. A key mechanism for RNA sensing is the discrimination between host and pathogen RNA to initiate antiviral responses. Interestingly, exoRNAs can also promote nonimmune cell activation. We have shown that stimulation of human normal and cancer cells with synthetic scrambled small interfering RNA (siRNA) or plant microRNA (miRNA) may modulate their secretory profiles, namely the production of pro-inflammatory cytokines. We also observed that the secretory phenotype was accompanied by changes in levels of the DNMT2/TRDMT1 protein belonging to the family of 5-methylcytosine (m^5C) RNA methyltransferases (m^5C-RMT). In humans, m^5C is incorporated into different RNA molecules by the action of seven members of the NOL1/NOP2/SUN domain (NSUN) family of proteins, namely NSUN1-7, and the DNA methyltransferase 2/tRNA methyltransferase 1 (DNMT2/TRDMT1). We have shown (preliminary results) that exoRNA that mimicked RNA releasing from drug-treated dying normal and cancer cells during chemotherapy can modulate cancer heterogeneity and the knockout (KO) of the *TRDMT1* gene may result in affected secretory profile and retrotransposon activity in osteosarcoma cells. In the present project, we proposed to test the hypothesis that m^5C-RMTs are essential factors during the cellular response to exogenous and extracellular RNA, and their activity is important for nonspecific immune responses of cancer cells exposed to foreign RNA. We would like to answer the following questions. Which of the m^5C-RMTs in nonimmune human cells is essential for a proper cellular response to exoRNA isolated from bacteria, pathogenic fungi and plants? Can extracellular RNA derived from dying or senescent cells modulate the phenotype of neighboring cells and can this effect be mediated by m^5C-RMTs? What types of extracellular RNA promote m^5C-RMT-mediated responses? Is the presence of functional m^5C-RMTs essential for the intracellular metabolism of synthetic RNA? Can exoRNA activate endogenous retrotransposons by changes in the levels of m^5C-RMTs? Several cellular models will be considered. For evaluation of the effect of exoRNA (bacterial, yeast, plant) on m^5C-RMT activation and related responses, human normal and cancer lung cells will be used as cells that have first contact with exoRNA. For evaluation of the effect of extracellular RNA from dying and drug-induced senescent cancer cells on the nonspecific immune response of cancer cells with functional and non-functional m^5C-RMTs, osteosarcoma cell lines will be used. Gene KO protocols will be applied to obtain cancer cells with non-functional m^5C-RMT gene. Cells will be stimulated with exogenous and extracellular RNA. Secretory phenotype, the activity of several pathways, cell invasiveness, migration, induction of cell senescence will be studied. RNA binding partners of m^5C-RMTs will be also identified. The ability of synthetic mRNA to induce genetic instability in osteosarcoma cells with non-functional m^5C-RMT gene will be also investigated. We will test if m^5C-RMTs can modulate the metabolism of synthetic mRNA and cells without m^5C-RMT can use it as a repair template. Cells will be passaged after transfection with synthetic mRNA for 30 days and then changes in the genome will be assessed to evaluate whether synthetic mRNA can be used in cells with inactive m^5C-RMT to repair endogenous damage. DNA damage response, the activity of the autophagy pathway as a pathway involved in the removal of RNA-protein complexes and retrotransposon activity will be also analyzed. We believe that our project will gain new knowledge on molecular mechanisms of m^5C-RMT action in cancer cells, especially as a response to exogenous and extracellular RNA. The obtained results will be interesting and useful for researchers focused on medical and biological sciences especially for molecular geneticists and molecular toxicologists.