One of characteristic features of cancer cells is genomic plasticity, namely the susceptibility to genomic changes that depends on both endogenous and exogenous factors. Genetic changes in cancer cells may reflect their adaptation strategies, especially during stress conditions, e.g., during anticancer therapy and/or cancer progression. These genetic changes may rely on both non-lethal gene mutations as well as chromosome alterations. Genomic plasticity may play an important role in the promotion of cellular heterogeneity that may lead to drug resistance of cell subpopulations. Chromosome changes may also stimulate the production of locally acting agents, namely growth factors and/or cytokines that may provoke inflammation and cancer progression. Telomeres may shape the dynamics of chromosome changes. Telomeres are tandem repeats of DNA sequences associated with proteins that protects chromosomes against damage and uncontrolled joining of free DNA ends. Telomeres may also maintain chromosome topology and regulate gene expression. In normal cells, telomere shortening below a critical value as a consequence of a number of cell divisions and/or damage may result in cell cycle arrest, senescence, apoptosis or genomic instability-based cancer transformation. In contrast to normal cells, in cancer cells, telomeres may be elongated due to re-activation of telomerase leading to cell immortalization. Telomerase is a ribonucleoprotein complex composed of reverse transcriptase subunit and RNA component. Telomerase activity is regulated by different molecular factors and at various levels, e.g., during gene transcription of both subunits, complex assembly and telomerase associations with telomere proteins (shelterin). The search for molecular factors regulating the formation of active telomerase complex is still needed. According to our preliminary results and literature data, we hypothesized that DNMT2 methyltransferase may be a new factor responsible for the modulation of telomerase activity and in turn may regulate telomere length and may lead to chromosome instability. Within proposed project, we would like to compare DNMT2 level-dependent chromosome and phenotypic variability including secretion profile and microRNA profile and the levels of TERRA (telomeric repeat-containing RNAs) in different cancer cells. Taken together, proposed project will provide important data on molecular mechanisms underlying cellular heterogeneity and genomic plasticity of cancer cells.