Mutator genes, genome stability

Spontaneous mutation rate in somatic cells alone is insufficient to account for the high number of chromosomal abnormalities and high number of mutations in human cancer. **Mutator phenotype** hypothesis suggests that next to proto-oncogenes and tumor suppressor genes there are mutations in genes that maintain the stability of the genome and drive tumor progression. The result of genomic instability is the accumulation of mutations that provide a survival advantage to specific clones of cells, which eventually could become carcinogenic. Mutator phenotype is achieved by the inactivation of so called **mismatch repair (MMR) genes**. These genes are important in maintaining the accurate repeat units of microsatellites. In the S-phase of the cell cycle, when DNA is replicated, polymerases are prone to errors in regions of high homology and low complexity (polynucleotide stretches like 20Ts, or dinucleotide stretches as (CA) repeats).

Mismatch repair genes code for proteins that are capable of mechanism to repair such errors. Repetitive sequences are located throughout the genome. Microsatellite mutations due to nonfunctional MMR genes may lead to genomic instability, which, in turn, may accelerate further accumulation of mutations in other cancer genes during tumorigenesis. Other mechanism increasing the tumor mutation burden are mutations in genes involved in **DNA repair pathways**. As samely as tumor suppressor genes, mutator genes have AD inheritance in human pedigrees and second mutation on somatic level is necessary for tumor progression.

A typical example is gene *MSH2*. People who are born with an inherited defect is this gene have a high risk of developing colorectal cancer (also endometrial or ovarian cancer) at relatively young adult age (around 40 years of age). This **Hereditary Non-Polyposis Colorectal Cancer** (HNPCC) or **Lynch syndrome** is caused by defect in MMR genes (not only *MSH2* (60%), but also *MLH1* (30%), or other genes) and leads to accumulation of microsatellite instability mutations in coding parts of other cancer causing genes (*APC, KRAS*,...). *APC* gene has a microsatellite block in its coding part, any mismatch in number of such block results in frameshift mutation leading to non-functional APC protein.

Proteins that act in human cells as protectors of genome stability and DNA fidelity are mainly polymerases with proofreading activity, DNA mismatch-repair protein complexes, or DNA glycosylases in base-excision repair pathway. When there is improper amount or changed function of these repair proteins cell is prone to DNA mutation accumulation.