Genome-wide analysis of copy number abnormalities and copy neutral-loss of heterozygosity and their relationship to chromosomal or microsatellite instability in colorectal cancer

Vincenza Barresi[1,2], Nicolò Musso[1], Carmela Capizzi[1], Giovanna Privitera[3], Tonia Luca[3], Sergio Castorina[3,4], Daniele Filippo Condorelli[1,2]

[1] Laboratory on Complex Systems, Scuola Superiore di Catania, University of Catania, Italy
[2] Department of Chemical Sciences, Section of Biochemistry and Molecular Biology, University of Catania, Italy
[3] Fondazione Mediterranea "G.B. Morgagni", Catania, Italy
[4] Department of Human Anatomy "GF Ingrassia", University of Catania, Italy

It is well-known that at least two forms of genetic instability have been observed in CRC: *chromosomal instability* (CIN), that is present in 85% cases and is characterized by structural and numerical chromosomal abnormalities (aneuploidy); and *microsatellite instability* (MSI), characterized by a deficiency of the mismatch repair system that leads to slippage in microsatellites, and associated to a normal or quasi-normal karyotype (euploidy). It is clear that such molecular classification has a clinical impact both in prognostic and therapeutic terms, but there is a substantial delay between novel molecular insights and established clinical practice. Recent advances in molecular cytogenetics techniques are likely to introduce a revolution in the field. In the present study we analysed a series of 42 colorectal cancer by high resolution genomic arrays (Affymetrix SNP 6.0 arrays) that allow the determination of an accurate genome-wide molecular karyotype using only 500 ng of DNA extracted from the tumor mass after colectomy. Moreover, all samples have been tested for microsatellite instability, by a specific PCR test followed by capillary gel electrophoresis according to NHI guidelines. MSI tumors represented 19% of our CRC series and showed a median values of copy number abnormalities (CNAs, DNA segments gains and losses) of 2.5 (range 0-6), while microsatellite stable (MSS) tumors showed a median value of 17 (range 0-35). Therefore all MSI tumors were below a threshold of 6 CNAs, while only 10% of MSS were below this threshold, representing a group of microsatellite and chromosomal stable tumors. No correlation was observed between the number of tumor associated CNAs and the number of somatic copy neutral-loss of heterozygosities (CN-LOH) regions, suggesting that different mechanisms may underlie such chromosomal abnormalities. Interestingly, a relatively high proportion of individuals bearing a high level of germ-line CN-LOH regions (a phenomenon called autozygosity) was observed in our CRC series, thus confirming recent data (Bacolod et al. 2009). These long homozygous chromosomal segments may be explained by the common ancestry of the individual's parents, suggesting that consanguinity may be a factor in colorectal cancer predisposition.

References

Bacolod MD et al. (2009) Emerging paradigms in cancer genetics: some important findings from high-density single nucleotide polymorphism array studies. Cancer Res., 69(3):723-7.

Key words
Colorectal cancer; CIN; MSI; SNP array