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HSP110: An unexpected target gene for instability in colorectal cancer

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Heat shock proteins (HSPs) are oncogenic proteins that enhance cancer cell survival and resistance to chemotherapy. It was recently described, the first mutation affecting a chaperone protein in a cancer so far. This mutation, i.e. somatic deletion of the T17 repeat within intron 8 of HSP110, is specific and occurred frequently in colorectal tumors displaying widespread microsatellite instability (MSI, 15-20% of all colorectal cancer). Decreasing length of the HSP110 T17 repeat correlated with increased synthesis of a mutant HSP110 isoform called HSP110DE9 as a result of exon 9 skipping. It led to abrogation of HSP110 chaperone activity and of its anti-apoptotic function. Forced overexpression of HSP110DE9 in colorectal cancer cell lines led to them becoming sensitized to chemotherapy. In both cell lines and primary tumors, it is shown that this situation occurs in a fraction of MSI samples owing to large deletions of the HSP110 T17 repeat that allows both the aberrant expression of HSP110DE9 mutant and the complete silencing of HSP110wt in tumor cells. HSP110 T17 mutations are usually biallelic in primary MSI CRCs. Careful examination of T17 status in a consecutive, multicentered series of patients whose positive MSI status was identified prospectively at the time of diagnosis confirmed that, in line with the molecular data, only patients with large T17 deletions (5 bp or more) and representing a minority but nevertheless important fraction of MSI CRC patients (i.e. about 25%) appeared to benefit from 5-FU–based adjuvant chemotherapy. Of particular interest, the association between survival and T17 deletion status remained significant in the subgroup of patients treated with 5-fluorouracil alone.

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