Expression of a dominant negative hsp110 mutant by colorectal cancer cells decreases their survival and improves patient prognosis

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Abstract

Heat shock proteins (HSPs) are necessary for cancer cell survival. We identified a mutated form of HSP110 (HSP110DE9) in colorectal cancer displaying microsatellite instability (MSI CRC), generated from an aberrantly spliced mRNA and lacking the HSP110 substrate binding domain. This mutant is expressed at variable levels in MSI CRC cell lines and primary tumors. HSP110DE9 impaired both the normal cellular localization of HSP110 and its interaction with other HSPs, thus abrogating the chaperone activity and anti-apoptotic function of HSP110 in a dominant negative manner. HSP110DE9 overexpression caused the sensitization of cells to anticancer agents such as oxaliplatin and 5-fluorouracil which are routinely prescribed in the adjuvant treatment of CRC patients.

The expression level of mutant HSP110 correlates with the size of allelic deletions in the HSP110 T₁₇ DNA repeat located in intron 8. We recently examined a consecutive, multicentre series of 329 patients with stage II or stage III CRC whose positive MSI status was prospectively identified at diagnosis using standardized methods. Both stage II and stage III CRC patients with large HSP110 T₁₇ deletions and who received adjuvant chemotherapy showed excellent relapse-free survival regardless of the regimen used. Multivariate models confirmed that the survival of stage III MSI CRC patients and of chemotherapy-treated MSI CRC patients was dependent on the mutation status of HSP110 T₁₇. Mutations in HSP110 T₁₇ thus predict the outcome of patients with MSI CRC. The likely mechanism for this association is the chemosensitization of cancer cells following the loss of HSP110 chaperone function.

Biography

Alex Duval is M.D. and he has completed his Ph.D at the age of 35 years from Paris René Descartes University and postdoctoral studies from French Institute of Health in the lab of Pr. Gilles Thomas in Paris. He is the director of the team ‘Microsatellite Instability and Cancer’, a research team whose activity is entirely dedicated to the study of MMR-deficient neoplasms. He has published more than 50 papers in reputed journals such as Nature Medecine, Journal of the National Cancer Institute, Journal of Clinical Oncology, Gut, Gastroenterology or PNAS.