Spinophilin, a new tumor suppressor at 17q21

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The scaffold protein spinophilin is a regulatory subunit of phosphatase 1a (PP1a) located at 17q21.33. This region is frequently associated with microsatellite instability and LOH and contains a relatively high density of known tumor suppressor genes (such as BRCA1), putative tumor suppressor genes, and several unidentified candidate tumor suppressor genes located distal to BRCA1. We have also recently found that Spn protein is lost in 20% and reduced in another 37% of human lung tumors. Furthermore, in animal models, loss of SPN increases tumorigenesis in vivo. We found that loss of Spn increases the onset of lymphoma in mice, and increases the aparition of mammary carcinomas in a mutant p53 background. To determine how loss of Spinophilin may contribute to tumorigenesis we explored the contribution of SPN to PP1a-mediated Rb regulation and their relationship to tumorigenesis. We found that the loss of Spinophilin downregulated PPP1CA and PP1a activity, resulting in a high level of pRb, which in turn, resulted in increased p53 activity through ARF. However, in the absence of p53, reduced levels of SPN enhanced the tumorigenic potential of the cells. Furthermore, the ectopic expression of SPN in human tumor cells from different types of malignancies greatly reduced cell growth. Taken together, our results show that the loss of Spinophilin induces a proliferative response by increasing Rb phosphorylation, which in turn activates p53, thereby, at least partially, neutralizing the proliferative response. The absence of p53 bypasses this barrier and enhances the malignant phenotype. Therefore, we suggest that Spinophilin may be the tumor suppressor gene that is located at 17q21.33, distal to BRCA1, and that its tumor suppressive function is dependent on the absence of p53.