ATR suppresses the pro-tumorigenic functions of breast stromal fibroblasts

The ATR protein kinase is a master regulator of the cellular responses to DNA damage and replication stresses. Despite these crucial physiological roles, the implication of ATR in human carcinogenesis remains elusive. We have shown here that the ATR level is reduced in most cancer-associated fibroblasts (CAFs) as compared to their adjacent normal counterparts. Importantly, specific ATR knockdown activated breast fibroblasts, and enhanced their paracrine pro-carcinogenic effects via strong increase in the expression/secretion of SDF-1 and IL-6. Furthermore, ATR-deficient fibroblasts enhanced tumor growth and aggressiveness in orthotopic breast tumor xenografts. On the other hand, ectopic expression of ATR suppressed the expression/ secretion of several cancer-promoting proteins such as IL-6, TGF-β1 and SDF-1, and inhibited the migration and invasion capacities of breast myofibroblast cells. Furthermore, ATR up-regulation in active breast fibroblasts reduced their paracrine pro-migratory/-invasive effects on breast cancer cells. Interestingly, the cancer promoting effects of ATR-deficient cells were repressed by ectopic expression of the ATR effector p53. These results indicate that ATR is a major target of cancer cells in breast fibroblasts wherein this protein kinase represses both autocrine and paracrine pro-carcinogenic effects. This indicates that the ATR status in these cells could be of great prognostic/diagnostic values