Novel Tumor-Suppressing Signal Pathways: A Window for Target-Specific Anti-Cancer Drug Development

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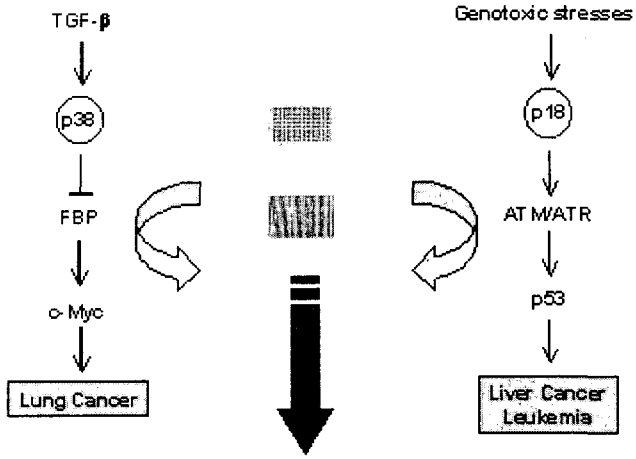
Most of the classical cancer drugs currently used accompanies severe side effects due to non-specific genotoxic or cytotoxic activities since they are not aiming at a specific target or mechanism related to the control of tumorigenesis. However, thanks to recent development in genome research, many new factors playing critical roles in the regulation of cell cycle and tumorigenesis have been revealed and these factors can be used as drug targets once their correlation with cancer are clinically validated. Here we report two novel tumor suppressors that play unique roles in the control of different types of cancer. A factor called p38/JTV-1 facilitates the TGF-beta signal pathway from the membrane to nucleus via direct association of R-Smads. In the nucleus, it suppresses abnormal increase of proto-oncogene, c-Myc, which is important for the inhibition of lung cell overproliferation. The tissue analysis of lung cancer patients demonstrated that p38/JTV-1 level was severely reduced compared to that in the normal cells at over 90% frequency, and the suppression of p38 induced cell transformation. Molecular investigation of lung cancer cells revealed that a tumorigenic variant of p38 is generated in cancer-specific manner, and the specific inhibition of this variant with siRNA technique restored cell control and TGF-beta signaling. We found that this variant makes a heterodimer with the functional p38, which subsequently undergoes degradation cycle. Knowing the working mechanism of p38 and its functional significance in tumorigenesis, we designed the drug screening system in which the generation of the tumorigenic variant of p38 or the interaction of its deadly interaction with the normal p38 is inhibited to maintain the normal p38 activity.



Target-specific Novel Anticancer Drugs

We also found another novel tumor suppressor designated as p18. The p18 loss-of-function mutation resulted in embryonic lethality, indicating its functional essentiality. Interestingly, while the live p18 heterozygous mice showed morphologically and anatomically normal, they spontaneously developed various tumors when they were aged. The p18 heterozygous cells showed higher cell growth rate and became insensitive to apoptotic response to DNA damage. The investigation on its working mechanism showed that p18 directly binds to and activates ATM/ATR that are critical kinases responding to DNA damage and upstream regulator of p53. The hypomutation of p18 was frequently observed in the patients of leukemia and liver cancer. Based on the phenotypes of p18 mutant mice, molecular mechanism and its association with human cancer cases, p18 can be classified as a novel haploinsufficient tumor suppressor. In this case, we designed the drug screening system in which we look for the drugs that can restore the normal activity of p18 and p53 activity. These drug-screening systems provide a new window through which anti-cancer drugs can be discovered that are completely different from classical toxic anti-cancer drugs. Nearly 10,000 synthetic and natural products have been screened through these systems and a few compounds with desired activities have been identified. Their *in vitro* and *in vivo* efficacy against cancer cells and tumors will be discussed in this presentation.