Kasai, Masataka [25]

Acceleration of cell division independent of increases in cell mass

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Although most cells maintain a constant size as they proliferate, it remains unclear how the cell cycle progression is coupled to increases in cell mass. We have previously identified a DNA-binding protein, Translin, whose native form consists of a ring-shaped structure with an assembly of eight 27-kD monomer subunits. This multimeric structure creates a DNA-binding domain for the sequences at breakpoint junctions in many chromosomal translocations. The region around the Translin gene on human chromosome 2q21 also harbors the *ERCC3* gene, which is known to be involved in human disorders of DNA repair. Despite detailed studies on protein–DNA interactions, the functional significance of Translin remains unknown. In studies comparing basal expression levels of Translin across various tissues and cell lines, we have found a good correlation between Translin protein synthesis and cell proliferation. To analyze the effect of Translin on cell proliferation, we established a Translin expression system regulatable by doxycycline. We found that overexpression of Translin in HEK293 cells increased cell proliferation by two- to threefold. Flow-cytometric forward-scatter analysis revealed that the size of the cells was increased compared with the control cells that grew in the absence of doxycycline. These results indicate that Translin may be involved in cell cycle progression and that its overexpression accelerates cell division independent of increases in cell mass.

Khan, Javed [26]

Development of a molecular taxonomy of small blue round-cell tumors using cDNA microarrays

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Many of the pediatric solid tumors categorized as small blue round-cell tumors (neuroblastoma, rhabdomyosarcoma, lymphoma and Ewing sarcoma) are difficult to distinguish morphologically, and routine immunohistochemistry may be insufficient to characterize them. Several specialized techniques are used to diagnose these cancers, including cytogenetics, interphase fluorescence *in situ* hybridization, the polymerase chain reaction with reverse transcription, and immunohistochemistry. However, despite the availability of these tests, poorly differentiated cancers can still pose a diagnostic dilemma. Gene expression profiling permits the simultaneous analysis of multiple markers, no one of which can perfectly classify any cancer. Based on our hypothesis that the gene expression profile is specific for each type, we have used complementary DNA microarrays containing 6,570 genes to investigate the expression profiles of 64 pediatric cancers. These included both tumor biopsy tissues (13 Ewing sarcomas and 11 rhabdomyosarcomas) and cell lines (10 Ewing sarcomas, 10 rhabdomyosarcomas, 12 neuroblastomas and 8 lymphomas). Using supervised clustering (*F*-statistics and weighted gene analysis), multidimensional scaling, hierarchical clustering, principal component analysis and layered perceptron prediction algorithms, we have identified 131 genes that accurately distinguish between these cancers. We have confirmed the accuracy of these findings in classification of these cancers on 12 blind samples. We have also identified several biologically relevant genes that are uniquely expressed in specific cancer types but that have not been previously associated with these diseases. Our results support the potential of cDNA microarrays as an efficient tool for developing a molecular taxonomy of cancer.

Kinoshita, Ichiro [27]

Identification of genes regulated by AP-1 in Rat-1a cells expressing inducible cJun

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A major component of the transcription complex AP-1 is cJun. Although upstream signaling cascades to this transcription factor have been well characterized, its downstream effector genes remain to be characterized. To identify cJun target genes, we established a conditional transformation system of Rat-1a cells using tetracycline-inducible cJun. Under adherent growth conditions, cJun expression was rapidly increased in 4 h, and morphological changes gradually occurred after 24 h (spindle and refractile phenotypes appeared after 24 h; close contact of cells, after 2 days; and piling up of cells, after 3 days). In addition, expression of cJun allowed Rat-1a cells to grow without a substratum (nonadherent growth). We identified differentially expressed genes from cJun-induced cells compared with uninduced Rat-1a cells using differential display, suppression subtractive hybridization and microarray analysis. We identified 27 upregulated and 8 downregulated cDNA fragment clones and confirmed 2- to 28-fold differences by northern blot analysis. Sequence analysis revealed 29 known genes and five unmatched clones in addition to *c-jun* itself. All 11 genes with known promoters had AP-1 sites, and 5 genes have been reported to be regulated by AP-1. Surprisingly, approximately 50% of the genes were identical to or showed homology with cytoskeleton- and adhesion-related genes, suggesting possible cooperative roles in morphological transformation. Furthermore, growth under nonadherent conditions altered the differential expression of some genes. We are currently investigating the precise roles of these genes.

Kirsch, Ilan [28]

The Cancer Chromosome Aberration Project: Update on BAC clone repository and database

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The Cancer Chromosome Aberration Project generates a repository of BAC clones with a resolution of 1–2 megabases. The cytogenetic location of all clones is established by high-resolution fluoresence *in situ* hybridization mapping onto