Special Summer 2004
F21C/Food Science & Engineering Unit
Seminar Series

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Title, Abstract: DNA microarray profiling for diagnostic and therapeutic targets

Gene expression profiles of a diseased state provide global insight into the molecules and biological processes perturbed in an otherwise homeostatic system. Oral premalignancy is an ideal stage of intervention that might allow us to achieve better management of the disease from progressing to malignant stages beyond which fatality rate remains obstinately stagnant. However, there is dearth of appropriate molecular targets and endpoint biomarkers that will improve therapeutic efficacy. We have investigated gene expression profiles of precancerous oral lesions in comparison to a less invasive variant of hyperplasia and carcinoma to identify genes that would help classify different stages of premalignant oral lesions in an early stage and help identify differentially expressed genes responsible for invasive behavior. We have performed AffymetrixTM gene chip based expression analysis of RNA transcripts from frozen paired normal and diseased tissues and validated few of the differentially expressed genes identified by real time PCR and immunohistochemistry analysis. We have identified around 1300 genes to be significantly (fold change = ±1.5 in 3 out of 4 comparisons) activated and 400 genes to be repressed. This differential gene expression was found to be statistically valid using Wilcoxon's signed rank test for detection P value = 0.0025., and change P value between 0.0 and 1.0 amongst 23,000 genes queried from the human U133A array. We have also analyzed the data for identifying the most perturbed biological pathway that might be responsible for oral malignant transformation. Based on such data, we have further validated a biological target of chemoprevention prostaglandin D2 synthase (PTGDS) in an oral cancer progression model cell lines as a negative regulatory gene in the arachidonic acid metabolism pathway, that might help prevent or delay progression by eliciting cell cycle arrest resulting in cell proliferation inhibition. We have also identified and validated two invasion related biomarkers psoriasin (S100A7) and versican (CSPG2) to be up regulated in oral premalignant and malignant tissues. Overall, we report a convergence of inflammatory pathways in malignant progression of oral premalignancy and hypothesize a central role of these processes that propels increased cell proliferation rates, angiogenesis and suppressed innate immune response mechanisms. Challenges faced in this kind of genomic profiling assays and future opportunities in developing real-time high throughput diagnostic systems using interdisciplinary systems biology approach will be discussed.

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