FEATURES

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Base Excision Repair in the Mitochondria

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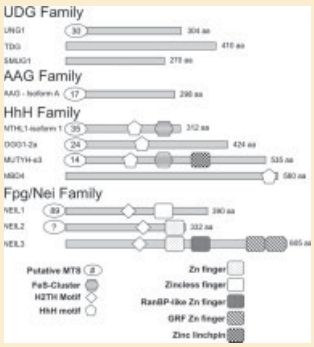
The 16.5 kb human mitochondrial genome encodes for 13 polypeptides, 22 tRNAs and 2 rRNAs involved in oxidative phosphorylation. Mitochondrial DNA (mtDNA), unlike its nuclear counterpart, is not packaged into nucleosomes and is more prone to the adverse effects of reactive oxygen species (ROS) generated during oxidative phosphorylation. The past few decades have witnessed an increase in the number of proteins observed to translocate to the mitochondria for the purposes of mitochondrial genome maintenance. The mtDNA damage produced by ROS, if not properly repaired, leads to instability and can ultimately manifest in mitochondrial dysfunction and disease. The base excision repair (BER) pathway is employed for the removal and consequently the repair of deaminated, oxidized, and alkylated DNA bases. Specialized enzymes called DNA glycosylases, which locate and cleave the damaged base, catalyze the first step of the highly coordinated repair pathway. The review focuses on members of the four human BER DNA glycosylase superfamilies and subcellular localization in the mitochondria and/or the nucleus, as well as summarizes structural features, biochemical properties, and functional role in the excision of damaged bases.



Vitamin D Control of Hematopoietic Cell Differentiation and Leukemia

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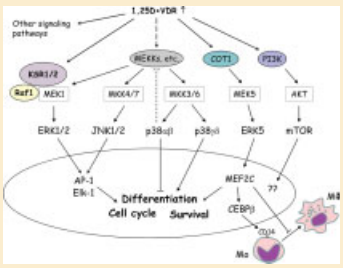
The authors present recent advances in current understanding of the role of 1,25-dihydroxyvitamin D (1,25D) in myelopoiesis and lymphopoiesis, and the potential of 1,25D and analogs (vitamin D derivatives; VDDs) for the control of hematopoietic malignancies. The reasons for the unimpressive results of most clinical studies of the therapeutic effects of VDDs in leukemia and related diseases may include the lack of a precise rationale for the conduct of the studies. Further, clinical trials to date have generally used extremely heterogeneous patient populations and, in many cases, small numbers of patients, generally without controls. Although low calcemic VDDs have been used and combined with agents that can increase the leukemia cell killing or differentiation effects in acute leukemias, the sequencing of agents used for combination therapy should to be more clearly delineated. Most importantly, it is recommended that in future clinical trials the rationale for the basis of the enhancing action of drug combinations should be clearly articulated and the effects on anticancer immunity should also be evaluated.



Journal of Cellular Biochemistry

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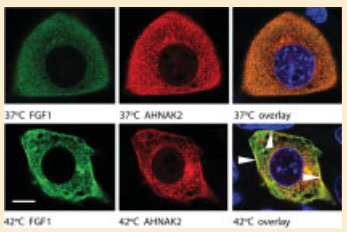
FGF1 is a nonclassically released growth factor that regulates carcinogenesis, angiogenesis, and inflammation. In vitro and in vivo, FGF1 export is stimulated by cell stress. Upon stress, FGF1 is transported to the plasma membrane where it localizes prior to transmembrane translocation. To determine which proteins participate in the submembrane localization of FGF1 and its export, the authors used immunoprecipitation mass spectrometry to identify novel proteins that associate with FGF1 during heat shock. The heat shock-dependent association of FGF1 with the large protein AHNAK2 was observed. Heat shock induced the translocation of FGF1 and AHNAK2 to the cytoskeletal fraction. In heat-shocked cells, FGF1 and the C-terminal fragment of AHNAK2 colocalized with F-actin in the vicinity of the cell membrane. Depletion of AHNAK2 resulted in a drastic decrease of stress-induced FGF1 export but did not affect spontaneous FGF2 export and FGF1 release induced by the inhibition of Notch signaling. Thus, AHNAK2 is an important element of the FGF1 nonclassical export pathway.



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The authors hypothesize that the observed differences in incidences of pleural and peritoneal malignant mesothelioma (MM) are the result of differences in the direct response of cell types to asbestos rather than to differences mediated by the in vivo microenvironment. The authors characterized cellular responses to asbestos in a controlled environment and found significantly greater changes in genome-wide expression in response to asbestos exposure in pleural mesothelial cells as compared to peritoneal mesothelial cells. In particular, a greater response in many common genes (IL-8, ATF3, CXCL2, CXCL3, IL-6, GOS2) was seen in pleural mesothelial cells as compared to peritoneal mesothelial cells. Unique genes expressed in pleural mesothelial cells were mainly proinflammatory (G-CSF, IL-1β, IL-1α, GREM1) and have previously been shown to be involved in development of MM. The results are consistent with the hypothesis that differences in incidences of pleural and peritoneal MM upon exposure to asbestos are the result of differences in mesothelial cell physiology that lead to differences in the inflammatory response, which leads to cancer.