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Aberrant regulation of oscillatory behavior in the extracellular signal regulated kinase (ERK) pathway: A toxicologists' perspective?

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Oscillatory behavior occurs in pathways central to toxicological responses, including ERK, NF-κB, p53-MDM2 and Ca^{2+}, however, the specific biological information encoded by oscillations is incompletely understood. We are the first to demonstrate that ERK oscillations regulate unique gene expression patterns in multiple experimental model systems, indicating that transcriptional regulation is one output for oscillatory behavior. We will discuss our most advanced experimental human model system that highlights a linkage between ERK oscillations and a transcriptional co-activator (MED1) whose half-life and activity is directly regulated by ERK-dependent phosphorylation as a feasible mechanism. Several toxicants (oxygen free radicals, ionizing radiation, bromate) inhibit ERK oscillations, and exploit well established stress-responsive signaling pathways (e.g. p38) to inhibit ERK signaling. However, the ERK feedback control processes specifically regulated by the stress response are undefined. We will also discuss experimental evidence that the inappropriate regulation of negative feedback loops in the ERK pathway can result in aberrant activation of ERK signaling, a response that has received little attention in a toxicological context. Finally, we have observed negative selection of ERK oscillations *in vitro* which may be important in view of the increased emphasis placed on *in vitro* screening assays in toxicology. Transcriptional misregulation is a mechanism frequently associated with toxic outcomes, therefore, the aberrant regulation of ERK oscillations by toxicants warrants further consideration in view of the unique gene expression profiles associated with this dynamic signaling behavior.

Biography

Thomas Weber completed his PhD at Texas A&M University followed by a NIEHS Post-doctoral fellowship at The University of Texas at Austin. He is currently a staff scientist at the Pacific Northwest National Laboratory. He has published 43 papers in reputed journals, 3 book chapters on cell signaling and protein phosphorylation in toxicology and a Reference Module in Biomedical Sciences (Elsevier publications). He is recipient of a US Patent, Federal Laboratory Consortium Award and R&D 100 award for development of technologies for cellular biomonitoring at the Pacific Northwest National Laboratory. Current projects in addition to studies on oscillatory behavior encompass molecular profiling of radiation resistance for consideration in clinical radiotherapy and medical countermeasures, development of lung organotypic platforms as toxicological screens and non-invasive biomonitoring using saliva as matrix.

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