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Learning to program the liver to protect us from chemicals

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Methodology for doing biological sciences, such as toxicology, has evolved markedly over the last 50 years. In the 1960s analytical methods for the toxicologist were not very specific or sensitive. To study a biological function, such as biliary excretion, one often had to select a surrogate chemical that could be quantified by color. However, techniques in analytical chemistry advanced much sooner than techniques to study functions and the effects of chemicals to organs and tissues. In the 1960s, to study the liver one was limited to use the intact animal or the isolated-perfused liver. Also in the 1960s, mainframe computers became available at major research universities, and toxicologists developed programs to organize and calculate their data. In the 1970s, techniques became available to isolate hepatocytes, and one could quantify the uptake of chemicals at very short time intervals and determine the mechanism of uptake of chemicals into the liver. It was not until the 1990s that the scientific community learned how to clone transporters, and then one could quantify the transcription of these genes and develop antibodies to quantify the transporter protein. From these and other techniques we are starting to learn how to program the liver. For example by giving chemicals such as the steroid PCN we can activate the PXR receptor which increases the Oatp transporters in the liver and thus decrease the toxicity of some chemicals taken up by this transporter and enhance the elimination of these chemicals from the body. Similarly be giving metals such as Cd or Zn we can enhance the amount of metallothionein in the liver and decrease the toxicity of Cd. We have also shown that a herbal chemical, oleanolic acid can activate the Nrf2 receptor and protect against the toxicity of a large number of chemicals because it increases enzymes that protect against oxidative stress and electrophiles. Thus, because of advancements in technology, we are starting to understand how to program the liver and other tissues, similarly as people were learning how to program computers a half century ago.

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Genome plasticity in a few lines: implications in human oncology

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An unexpected discovery to emerge from the Human Genome Project is that the human genome contains far fewer genes than originally postulated, with nearly half of the human genome constituted by repetitive sequences. Some of these repetitive sequences encode non-coding RNAs, while others encode proteins used to support the functionality of repetitive elements. A number of repetitive sequences in the human genome can potentially move to new locations and have therefore, been termed mobile transposable elements. LINE-1 is the most active mobile element of the human genome. This long interspersed nuclear element is silenced by via epigenetic mechanisms involving histone covalent modifications and DNA methylation that repress expression in somatic cells to maintain tight control of genomic integrity. Recent studies in the Ramos laboratory have shown that stressful cellular microenvironments modify the chromatin landscape to facilitate recruitment of proteins that mediate reactivation and mobilization of L1. At its most fundamental level, L1 mobilization induces insertion mutations and deletions, DNA breaks and splicing alterations, and increases the frequency of genetic recombination. These modifications define genome architecture, mutability and cellular programming, and can be of major clinical relevance in defining the genetic basis of human disease. The occurrence of L1 polymorphisms in the human population coupled to the reactivation of L1 may define the plasticity of the genome and individual differences in susceptibility to various forms of chronic disease and cancer.

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Nuevas fronteras en la investigación de las micotoxinas

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Las micotoxinas son metabolitos fúngicos que cuando son ingeridos, inhalados o absorbidos a través de la piel causan patologías de diferente importancia en hombres y animales, pudiendo llegar a desembocar incluso en la muerte. Desde el descubrimiento de las aflatoxinas en la década de los años 60 del pasado siglo, la investigación en micotoxicología ha sufrido un desarrollo notable, habiéndose caracterizado centenares de estos compuestos tóxicos. No obstante, en la UE solo se ha legislado su nivel en los alimentos en unas pocas micotoxinas, concretamente las aflatoxinas, ocratoxina A, patulina, zearalenona, fumonisinas, deoxinivalenol, toxinas T-2 y HT-2. De estas toxinas se ha ido conociendo numerosos datos sobre los mohos productores, su presencia en los alimentos y su toxicidad en el hombre y los animales, así como se han ido desarrollando métodos analíticos cada vez más sensibles y precisos. En esta conferencia se va a abordar dónde se encuentran actualmente algunas de las nuevas fronteras en las que se está desarrollando la investigación en este campo. Así, por un lado, se va a contemplar cuáles son las denominadas micotoxinas emergentes, aquellas de reciente caracterización que están siendo investigadas más detenidamente dado su potencial para ser consideradas en el futuro como micotoxinas importantes, entre las que destacan la beauvericina, las enniatinas, la moniliformina y la fusaproliferina. Por otra parte, se abordará el problema de las denominadas micotoxinas conjugadas (*masked o bounded mycotoxins*), compuestos derivados a partir de las micotoxinas por el metabolismo de las plantas, de los mohos o por el procesado de los alimentos, que pueden tener un comportamiento químico (por lo que pueden escapar fácilmente a los análisis de rutina) y una biodisponibilidad distinta a la de la toxina original, o pueden regenerar las moléculas nativas en el tracto gastrointestinal de los seres vivos, lo que puede tener repercusiones tanto desde el punto de vista toxicológico como legislativo.

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