Environmental toxicants like lead, mercury target stem cells

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Low levels of toxic substances cause critical stem cells in the central nervous system to prematurely shut down. That is the conclusion of a study published today in the on-line journal *PLoS Biology*. This research, which is the first to identify a common molecular trigger for the effects of toxicant exposure, may give scientists new insights into damage caused by toxicant exposure and new methods of evaluating the safety of chemicals.

While scientists have long understood that certain chemicals like lead and mercury have adverse effects on the body, the precise molecular mechanism by which many of these substances cause harm remain uncertain. This makes it more difficult to concretely link individual toxic substances with specific diseases or determine – with greater confidence – whether or not a chemical is toxic. However, recent advances in molecular biology, genetics, and stem cell biology have provided scientists a new window onto the impact of toxic substances on the cellular and molecular level.

"Establishing the general principles underlying the effects of toxicant exposure on the body is one of the central challenges of toxicology research," said University of Rochester biomedical geneticist Mark Noble, Ph.D., senior author of the study. "We have discovered a previously unrecognized regulatory pathway on which chemically diverse toxicants converge and disrupt normal cell function."

Noble and his colleagues exposed a specific population of brain cells to

low levels of lead, mercury, and paraquat, one of the most widely used herbicides in the world. These cells, called glial progenitors, are advanced-stage stem cells that are critical to the growth, development, and normal function of the central nervous system. The activity of cells is regulated by molecular pathways – or controlled chemical reactions – normally set off when substances bind to receptors on the cell's surface. Noble and his colleagues found that these compounds turned off specific sets of receptors and set into motion a molecular chain reaction that causes the cells to shut down and stop dividing.

"These toxicants are activating a normal cellular regulatory pathway, they are just activating it inappropriately," said Noble. "If this disruption occurs during critical developmental periods, like fetal growth or early childhood, it can have a significant impact. Development is a cumulative process, and the effects of even small changes in progenitor cell division and differentiation over multiple generations could have a substantial effect on an organism."

This study is an example of the ability of stem cell research to shed new light on many diseases and health problems that have heretofore been poorly understood by the medical community. Noble and his colleagues are pioneers in the field and have been involved in the discovery of several of the progenitor cells that are involved in building the central nervous system. The growing knowledge of the precise timing and role of these cells has enabled scientists to explore the molecular origin of these diseases, and the Rochester team's findings are part of a growing number of discoveries that indicate that certain developmental syndromes may be the result of disruption in stem cell function.

There are tens of thousands of synthetic industrial chemicals, pesticides, metals, and other substances for which toxicological information is limited or nonexistent. By identifying a molecular target that is shared by toxic substances, all with very different chemical compositions, this

discovery may give scientists a method to rapidly evaluate compounds to determine whether or not they pose a potential health threat.

"One of the obstacles in the analysis of new chemicals is the difficulty in developing a system that is sensitive enough and can make predictions that are true for both individual cells and the entire organism," said Noble. "This novel pathway gives as a way to analyze a diverse array of chemicals at levels in which they would be encountered in the environment. Furthermore, by identifying a specific molecular pathway that is activated by toxic exposure, we can now begin to look at specific ways to protect cells from this disruption of signaling."

Source: University of Rochester Medical Center