Paternal diabetes and offspring birth weight

The association between low birth weight and increased risk of non-insulin-dependent diabetes is well established, although the underlying mechanisms are not well understood. It has been suggested that shared genetic factors determine both sub-optimum prenatal growth and the risk to develop non-insulin-dependent diabetes later in life. If this would be the case, parental diabetes could be expected to be associated with a lower birth weight in the offspring. Using data from a large study of British births in 1958, we investigated whether a father’s non-insulin-dependent diabetes or a mother’s diabetes diagnosed after childbirth was associated with the birth weight of their offspring. In our study the offspring of the fathers with diabetes weighed significantly less than other children. Father’s adult height or social class could not explain this association. In agreement with earlier studies, maternal diabetes was associated with higher offspring birth weight. However, when the analysis was restricted to births occurring at least 10 years before the diagnosis of the mother’s diabetes, there was a suggestion of reduced offspring birth weight. These findings support the hypothesis that common genetic factors contribute both to the risk of non-insulin-dependent diabetes and decreased prenatal growth.

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Spinal neurones that mediate hyperalgesia

We found that a strong noxious stimulus may change the way the central nervous system handles subsequent nociceptive messages. Previously harmless noxious stimuli may now evoke strong pain-related responses. A small, but well-defined group of neurons in the spinal dorsal horn plays a key role for this form of “central sensitisation”. These neurons have a receptor for substance P, a neuropeptide that is released from nociceptive nerve fibers in spinal dorsal horn upon strong noxious stimulation. In addition, the neurons have an ascending projection to the brain. When a strong noxious stimulus is applied, substance P is released in addition to the classical neurotransmitter glutamate. Together they trigger cellular changes that lead to a long-lasting form sensitisation. The cause for this sensitisation is an enhanced transmission from nociceptive nerve fibers (mainly so called C-fibers) onto the spinal dorsal horn neurons.

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ATM—the first step in helping cells deal with DNA damage

Exposure to radiation and many other environmental toxins cause breaks in the DNA of cells. Cells must respond to these breaks by triggering a series of biochemical reactions that lead to repair of the damage. Otherwise, the damage may lead to genetic mutations that cause diseases, such as cancer. This vulnerability of cells to DNA breaks is why radiation poses a threat to astronauts in deep space, unprotected by the atmosphere; to soldiers or civilians exposed to radiation released by a blast of a nuclear weapon; and to individuals exposed to certain toxins in the environment. However, this same vulnerability of DNA is why physicians often use radiation as one form of treatment for many tumors. Our laboratory has been studying the role of a molecule called ATM (“Ataxia-telangiectasia, mutated”) in helping cells respond to DNA damage caused by radiation. Work from our lab and others in the past few years have demonstrated that once activated, the ATM protein kinase sets off a biochemical chain reaction that affects progression of cells through the cell cycle and repair of the damage to the DNA. A recent publication from our laboratory elucidated the mechanisms by which DNA damage activates the ATM kinase and initiates these critical cellular signaling pathways. Activation of ATM occurs via an intermolecular autophosphorylation event that disrupts an inactive ATM dimer and releases ATM monomers to phosphorylate numerous substrates in the cell. The generation of an antibody that specifically recognizes the phosphorylated and activated forms of ATM provides an extraordinarily sensitive marker of cells which have been exposed to DNA damaging agents. This antibody may be useful as a biomarker of human exposure to irradiation or other toxic insults. This also represents a novel mechanism of protein kinase regulation, and the activation signal itself appears to arise from alterations in higher order chromatin structure rather than from direct effects of DNA strand