100 YEARS AGO

A series of tables, showing the differences between Greenwich mean time and the civil times used in various parts of the world, compiled by Prof. John Milne, F.R.S., is published in the February number of the *Geographical Journal*. The names of places in the tables are arranged in alphabetical order, and the amount by which the time used at each is fast or slow of Greenwich mean time is indicated. ... It is pointed out that the Chinese at most places use an approximate apparent solar time, obtained from sun-dials. At Tientsin the civil time is determined by the municipal chronometer, which, however, has sometimes been known to have an error of three minutes. The Persians keep sun time, watches being set at sunset. In Teheran there is a midday gun fired by the time shown on a sun-dial. But a few minutes makes no difference in Persia; the railway trains start when full or when required, and Persian telegraphists do not give time of issue or receipt of telegrams.

From *Nature* 9 February 1899.

50 YEARS AGO

The nucleic acids and their derivatives are fundamental constituents of biological systems; but until recently workers have lacked precise micro methods for their study. Vischer and Chargaff, and recently Hotchkiss and also Reichard, have shown that partition chromatography may be used to separate and characterize certain derivatives. The methods employed by these workers to detect the spots on the chromatograms were, however, either limited in their scope or necessitated the analysis of a large number of fractions selected arbitrarily from the columns. We have approached this problem in a different way. Purine and pyrimidine derivatives are characterized by an intense ultra-violet light absorption in the region of 2650 A., and they can be detected in amounts of 10 μgm. or less by a simple photographic technique.– Roy Markham, John D. Smith

From *Nature* 12 February 1949.

Many more extracts like these can be found in *A Bedside Nature: Genius and Eccentricity in Science, 1869–1953*, a 266-page book edited by Walter Gratzer. Contact Lisa O'Rourke. e-mail: l.orourke@nature.com

elvis@head-cfa.harvard.edu

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Cell adhesion

New way to activate caspases

Erkki Ruoslahti and John Reed

Most cells need to be attached to a self-produced external meshwork known as the extracellular matrix in order to survive — without such anchorage they undergo apoptosis[1]. The cells attach through integrins, heterodimeric membrane proteins that link the intracellular cytoskeleton with the extracellular matrix. Many of the 25 or so known integrins recognize a tripeptide, arginine–glycine–aspartate (or RGD in single-letter code), in target proteins of the extracellular matrix[2]. And on page 534 of this issue, Buckley *et al.*[3] provide a startling new interpretation for the role of these RGD peptides in apoptosis.

In vitro experiments have shown that small peptides containing the RGD motif bind to integrins and, when presented to a cell in a soluble form, inhibit cell attachment. According to current thinking, the peptide-blocked integrins cannot provide the signals that cells would receive from matrix-bound integrins, resulting in changes in cell shape and, ultimately, apoptosis[1,4]. Because RGD-

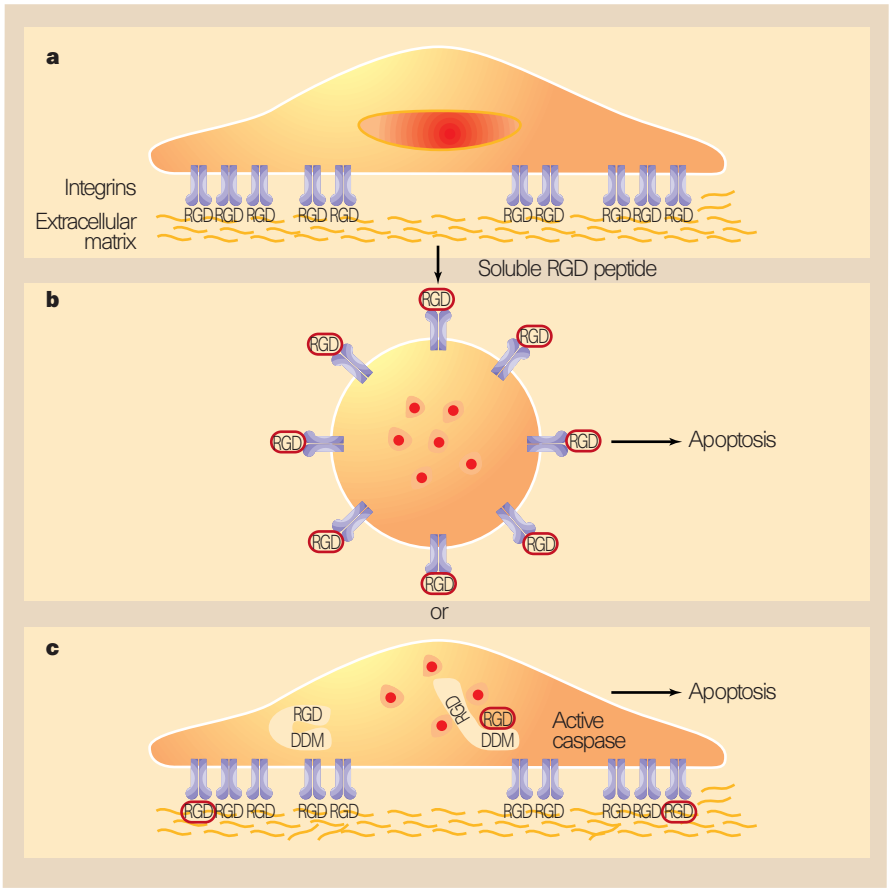

Figure 1 **The arginine–glycine–aspartate (RGD) peptide in apoptosis.** a, **Many cells attach, through integrins, to a substrate such as the extracellular matrix in order to survive.** b, **Addition of soluble RGD peptides causes apoptosis. One model is that the soluble peptides block integrin signalling to the extracellular matrix, so the cell detaches and the missing integrin signal causes apoptosis.** c, **Buckley *et al.*[3] propose a new explanation. They show that soluble RGD peptides cause apoptosis by activating procaspase-3 inside the cell. The RGD peptide may out-compete an RGD motif in the procaspase, blocking an intramolecular interaction with the sequence DDM and causing the pro-caspase to open up and be activated.**

based anti-thrombotic drugs are already in clinical use, and RGD drugs to treat osteoporosis and inhibit angiogenesis (the development of new blood vessels) are under development[2], knowing how these peptides act is of considerable importance.

The mechanism proposed by Buckley *et al.*[3] is that the soluble RGD peptide activates a caspase in the cytoplasm of the cell. Caspases are proteases that are critical in apoptosis. They amplify and propagate apoptotic signals and execute the apoptotic programme by degrading intracellular proteins vital for cell survival[5]. So, activation of caspases would be an alternative explanation for the pro-apoptotic activity of RGD peptides. The authors note that there is an RGD sequence near the active site of caspase-3 — the caspase that is reportedly activated by RGD peptides. They surmise that this RGD site is normally engaged in an intramolecular interaction, which keeps the procaspase inactive. But a soluble RGD peptide could block this intramolecular interaction, leaving the procaspase RGD site free. The procaspase could then open up (see Fig. 1) and be activated by, for example, self-digestion.

Supporting this proposed mechanism, the sequence aspartate–aspartate–methionine (DDM) — which resembles an RGD binding site in integrin β-subunits[6] — is found in a loop region of procaspase-3 that is proteolytically cleaved during activation. Unfortunately, the authors did not test whether the DDM peptide can activate caspases, nor did they mutate the DDM site in caspase-3 to test their hypothesis (mouse caspase-3, for example, contains the sequence glutamate–glutamate–methionine, EEM). Although the crystal structure of active caspase-3 is known[7], the structure of the unprocessed pro-form is needed to confirm the speculation about an intramolecular interaction between RGD and DDM.

Buckley *et al.*[3] have shown that RGD peptides specifically activate procaspase-3 isolated from cells by immunoprecipitation, and experiments using recombinant, purified procaspase-3 should be useful in working out the mechanism. One puzzling result from the experiments with intact cells is that integrins do not seem to be needed for internalization of RGD peptides — a RAD peptide, which does not bind to integrins[2], was also internalized by the cells. Integrins tend to transport ligands into the cytoplasm; viruses and intracellular bacteria use integrins as receptors, and gene therapists build viruses that do the same[2]. On this basis, we would expect only the RGD peptide to find its way into the cytoplasm.

Intriguing as this new mechanistic insight into the RGD peptide is, it is unlikely to be the whole story. For example, it is difficult to explain the pro-apoptotic activity of anti-integrin antibodies[8] on this basis. This activity seems to be tied to the specificity of the antibodies for an individual integrin, and not all of the antibodies contain an RGD sequence. It seems more plausible that these antibodies act through extracellular inhibition of cell attachment, rather than through direct activation of caspases within the cell. But there may be a way to reconcile the two mechanisms. Perhaps, when cells become detached from the extracellular matrix, RGD-containing proteins that would normally be used to replenish the matrix are degraded, and generate enough RGD peptides for caspase activation. In this regard, it would be informative to test the effect of anti-integrin antibodies on lymphocytes, which do not require attachment and do not make a matrix.

Buckley and colleagues' results open other fascinating possibilities. Could the HIV Tat protein, which is taken up by cells and contains an RGD sequence in one of its permutations, activate caspases? Could the anti-angiogenic compounds angiostatin and endostatin, for which no cell-surface receptor has been found, also act in this manner? Could RGD peptides with different integrin-binding specificities[2] differ in their abilities to activate individual caspases? (Buckley *et al.* used RGD peptides that bind to all RGD-directed integrins.) Could degradation of proteins from the extracellular matrix generate enough RGD peptide to cause apoptosis of cells in an involuting tissue, such as breast tissue that has stopped lactating[9]? Finally, can the RGD-mediated activation of caspases be exploited to trigger apoptosis selectively in cancer cells or inflammatory cells, without toxicity? The new work will stimulate much research along these lines. □

Erkki Ruoslahti and John Reed are at The Burnham Institute, 10901 North Torrey Pines Road, La Jolla, California 92037, USA.
e-mails: ruoslahti@burnham-inst.org
jreed@burnham-inst.org

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Photochemistry

Electronic motion in DNA

Mark Ratner

DNA's biological task involves information storage and propagation. To perform its function effectively, DNA must be stable, robust and repairable. Unlike proteins such as cytochromes and the photosynthetic reaction centre, DNA is not primarily an electron-transfer species. Still, the structure of DNA with its π-electron system of four bases stacked upon each other is reminiscent of certain molecular metals, such as doped phthalocyanines, so the possibility of long-range charge transfer is an intriguing one. Consequently, there has been a series of tantalizing reports on electron transfer in DNA. A new paper in the *Journal of the American Chemical Society* by Meggers *et al.*[1] reveals some regularities in the step-wise motion of electron 'holes' in the DNA structure, measures the length dependence of such transfers, and makes some general

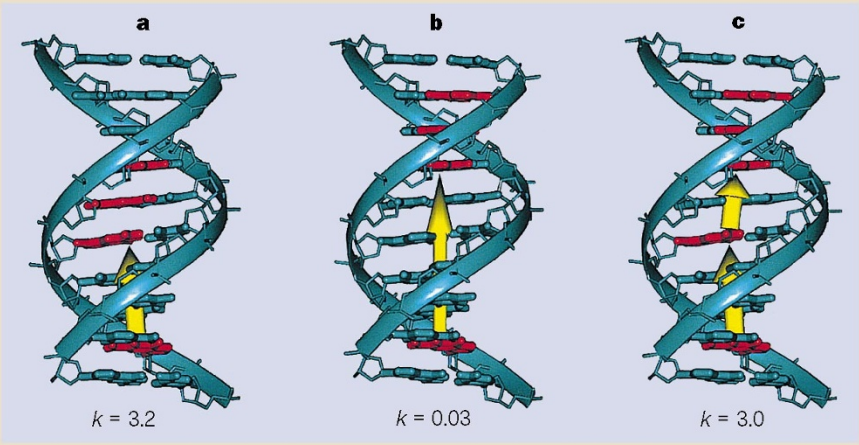

Figure 1 **Conduction in double-stranded DNA measured by Meggers *et al.*[1]. In** a, **an electron 'hole' passes from a guanine in a guanine–cytosine (GC) base pair (red) to another G by way of superexchange, jumping over two intermediate adenine–thymine (AT) pairs (blue). The rate of hole transfer *k* is shown below. In** b, **the superexchange transports the hole twice as far, but the transfer is 100 times as slow; whereas in** c, **two short superexchange hops by way of an intermediate G cover the same distance as in** b, **but as quickly as in** a. **The transfer from one G to the next occurs coherently (superexchange), but the transport over several G bases occurs incoherently (hopping).**