more powerful than a Turing machine, and has been proposed as just the right one to simulate natural physical phenomena. One hopes that the work of Gu *et al.*[3], along with these two ideas, will lead to a better understanding of the 'computer' in which we live. ■

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SYSTEMS BIOLOGY

When it is time to die

Philippe Bastiaens

Why do cells of the same population respond differently to external death-inducing stimuli? Individuality seems to originate from non-genetic differences in the levels and activation states of proteins.

Any cell biologist can tell you that individual cells from a clonal cell population respond differently to the same stimulus, some not responding at all. In such cases the percentage of responders is seen as a measure of the experimenter's control over parameters that affect the stimulus, such as uniformity of the cellular environment. Variability in cell response can have grave implications. For instance, some tumour cells refuse to die in response to drugs that trigger programmed cell death (apoptosis), affecting the efficacy of chemotherapy. In this issue, Spencer *et al.*[1] (page 428) show that the non-uniform response of a human cell population to the apoptotic stimulus TRAIL can be ascribed to an intrinsic random factor: the naturally occurring differences in protein-expression levels.

To induce apoptosis, TRAIL binds to the cell-surface receptors DR4 and DR5, triggering specific intracellular signalling pathways. These receptors are therefore attractive targets for the development of anticancer drugs, and several compounds that can activate them have been tested in preclinical and in phase I clinical trials, with some promising results[2]. DR4 and DR5 are expressed in normal as well as cancerous tissues, although there is some indication that tumour cells might have higher levels of these receptors[2]; at least, the compounds tested in the trials selectively induce apoptosis in tumour cells. Nonetheless, significant problems remain, including resistance and differences in sensitivity to TRAIL, and fractional killing — situations in which successive cycles of chemotherapy kill only some of the tumour cells[3].

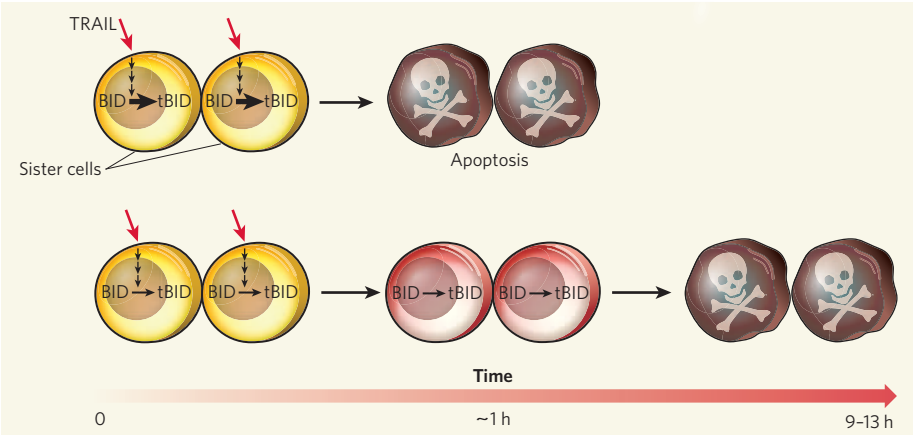

Figure 1 | Non-genetic factors contribute to the rate of apoptosis. Spencer *et al.*[1] find that different sets of sister cells respond differently in the time they take to die after exposure to the apoptotic stimulus TRAIL. The rate of response to TRAIL depends on the rate of proteolytic conversion of the pro-apoptotic protein BID to its active form tBID, which itself is affected by variance in the expression levels of several proteins in the early apoptotic machinery (vertical black arrows). The protein levels are inherited by daughter cells (which become neighbouring sister cells) causing them to behave similarly in response to TRAIL.

Spencer *et al.*[1] show that, in a cancer cell line, TRAIL induces a non-uniform response: some cells die within 45 minutes, some 8–12 hours later, and yet others do not die at all. Intriguingly, following exposure to TRAIL, recently born sister cells die after a similar period of time, suggesting that variability in the population arises from inherited cell differences before treatment with TRAIL (Fig. 1). The authors also find that, on inhibition of protein synthesis, the 'sisterhood' memory persists for longer, an observation that relates a non-genetic factor — protein expression — to variability in cell responses. Finally, they use computer simulation of a biochemical reaction model for apoptosis[4]. The stimulation used as input differences in the levels of proteins mediating apoptosis and the range in 'death times' the authors detect using this method match those they observed experimentally[1].

To investigate the molecular basis of variable cellular responses to TRAIL, Spencer and colleagues grouped the apoptotic protein machinery into three tiers: those occurring before, during and after the process of mitochondrial outer-membrane permeabilization (MOMP), which is crucial for apoptosis. In the first reaction tier, TRAIL binds to its receptors and leads to their association; the death-inducing signalling complexes (DISCs) assemble; and the proteolytic initiator-caspase enzymes become active to trigger MOMP. In the second reaction tier, during MOMP, mitochondrial proteins such as cytochrome *c* and SMAC are released into the cytoplasm. There, they activate effector caspases in the post-MOMP third reaction tier, causing cell death. The authors could microscopically image the activity of these mediators from each of the three tiers in single cells with genetically encoded fluorescence indicators[5] for both caspases and MOMP.

They find that variability in the time to death was almost exclusively determined by differences in the reaction rate of the initiator caspases, which convert a pro-apoptotic protein called BID into its truncated active form (tBID) in the first reaction tier (Fig. 1). tBID then induces the self-assembly of two pore-forming proteins, BAX and BAK — an activity that is normally prevented by its interaction with the anti-apoptotic proteins of the BCL2 family — into mitochondrial pores, thereby initiating MOMP. The authors therefore conclude that time to death is set by the rate of approach to a threshold in the levels of activated tBID at which mitochondrial pores form.

Spencer *et al.* argued that the levels of proteins functioning in the first reaction tier (DR4, DR5, DISC components, the initiator caspases 8 and 10, and BID) should determine the reaction rate for BID activation. But the authors' computer-simulation data show that the level of any one protein in the first tier does not determine time to death. Only on increased expression of one of these components did the

computer simulations detect a clear relationship between protein level and time to death — a finding that the authors verified experimentally by overexpressing a fluorescent BID protein. They therefore conclude that, under normal conditions, variations in the expression of several proteins together control the rate of approach to MOMP and so cell death.

Does this mean that several different states of the protein network in the first tier give rise to the same rate of approach to MOMP? To relate network states to time to death, the correlation between multiple protein levels and time to death must be investigated, rather than correlations involving single proteins as studied by the authors (using simulations).

Spencer and colleagues' work for the first time relates variability in molecular processes determined by protein-expression levels to variability in phenotypic response in human cells. However, it is not clear how the short-term memory ($t_{1/2}$ = 1.5 hours) for the rate of approach to MOMP can account for fractional killing in a cell population that has a typical doubling time of 20 hours. If protein levels fluctuate during this short time window, then successive TRAIL administrations should eventually kill all cells because of the high probability that the cells will experience the protein-network state favouring rapid apoptosis before they divide. Thus, optimized TRAIL-administration schemes could be devised to maximize the killing of tumour cells. Nevertheless, the ultimate cell-fate decision, to die or not to die, might eventually lie in the expression level of anti-apoptotic proteins, such as those of the BCL2 family, that set the threshold in the system. ■

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EARTH SCIENCE

Life battered but unbowed

Lynn J. Rothschild

Early in its history, Earth experienced a pounding from extraterrestrial impacts. But instead of sterilizing the planet, it allowed microbial life to persist, according to numerical models of Earth's crust.

The great baseball player Leroy 'Satchel' Paige, who pitched professionally until the alleged age of 60, asked "How old would you be if you didn't know how old you were?". It was a reasonable question, given that his year of birth was unknown. Much the same applies to the age of life on Earth. If you are comfortable thinking that we Earthlings must be younger than 3,900 million years, the paper by Abramov and Mojzsis[1] on page 419 of this issue will come as a shock. We may be several hundred million years older than that.

The current narrative of Earth's history begins about 4,600 million years (4.6 Gyr) ago when the planet formed. Within 100 million years, the young Earth suffered its worst day ever with the impact of another — rogue — planet, the debris from which ultimately formed the Moon. Even if Earth had cooled substantially before the lunar-forming impact, the heat of the impact would have melted Earth's surface[2]. For another 600 million years, especially during the late heavy bombardment (LHB) — roughly 4.1–3.9 Gyr ago — Earth was pummelled by impactors (Fig. 1), mainly asteroids, that heated up both land and oceans. Few, if any, rocks remain from before the end of the LHB, with the oldest currently known being from 4.03 Gyr ago[3], and with the earliest, albeit controversial, isotopic fossil evidence for life at 3.8 Gyr ago[4].

Geological models[5] have suggested that Earth could not have been continuously habitable during this period, because there was insufficient time for the origin of life between impacts. Furthermore, estimates[6] of the last impact that sterilized the oceans range from 3.8 to 4.44 Gyr ago. This left biologists with the tantalizing but impenetrable possibility that life originated more than once, and that the present lineage of all life — the prokaryotic archaeans and bacteria, and eukaryotes such as ourselves — stems from a later incarnation. This view implies that life arose quickly, because there is isotopic evidence for its origin within 100 million years of the end of the LHB. Alternatively, life on Earth originated elsewhere, Mars for example.

NASA/JPL/USGS

Figure 1 | Impact evidence on the pock-marked face of the Moon. The late heavy bombardment is thought to have affected all bodies in the inner Solar System. On Earth, traces of the impacts have been erased by surface geological processes. But on the Moon many craters date to that time, and are still visible.

This story began to change with the discovery of zircons that pre-date the LHB. Zircons are telltale mineral inclusions in ancient rocks, and the evidence from them supported the idea of a Hadean era (4.38–3.85 Gyr ago) that was far from hellish, with liquid water, crustal recycling, a granitoid crust and low-temperature processes occurring at the boundaries of tectonic plates[7,8].

What if the period since the lunar-forming impact, including the LHB, was never severe enough to sterilize Earth? This is precisely what Abramov and Mojzsis[1] suggest. On the basis of numerical models of impact-generated heat in Earth's crust, they propose that, at worst, only 37% of Earth's surface was sterilized, and less than 10% experienced temperatures above 500 °C. They conclude that, even if all of the LHB impacts occurred simultaneously, Earth would not have been sterilized. The likelihood of finding life on planets with an equally strong impactor record, such as Mars, or maybe even extrasolar planets, has just improved.

The study[1] is based on several assumptions. The first is that life was distributed over the surface and subsurface of Earth by events during the LHB. Of course, there is no evidence for this, but today organisms up to 1–2 millimetres in size are globally dispersed by wind, oceanic circulation and groundwater networks[9], processes that would also have occurred