Perspectives on Quality

The DNA damage response and patient safety: engaging our molecular biology-oriented colleagues

KARIN PUKK1 AND DAVID C. ARON2

1Medical Management Center, Karolinska Institute, Stockholm, Sweden, 2Division of Clinical and Molecular Endocrinology, Case Western Reserve University School of Medicine, and 3VA HSR&D Center for Quality Improvement Research, Louis Stokes Cleveland, Department of Veterans Affairs Medical Center, Cleveland, Ohio, USA

Abstract

The imperative to improve patient safety is clear. Biomedical scientists, who account for a large proportion of medical school faculty, and clinicians tend to speak different languages. Biological systems are remarkable for their high robustness, flexibility, and efficiency. Biomedical scientists possess a profound understanding of the complex mechanisms that govern organisms. Their insights may inform the design of safer health care systems. We propose a model to assist in bi-directional communication between these disciplines. We use the principles and mechanisms of the DNA damage response to describe the central concepts of safety science and discuss similarities and differences between the systems of DNA repair and organizational approaches to safety in health care. We suggest that such biomedical scientists can and should be engaged in the effort to bring education about patient safety management into the medical school curriculum and to make patient care safer.

Keywords: complexity, DNA repair, medical education, patient safety, systems thinking

Medical schools have responsibility for preparing every graduate to practice medicine in ways that ensure the safety of patients, but have fallen short [1,2]. A number of factors in medical education that allow for the graduation of students unable to practice safely or improve their care have previously been identified [3]. We suggest that another contributing factor is the difficulty of integrating basic science, the science of normal disease biology, and clinical medicine, the science and art of practice. This issue has underlain much of the effort in curricular reform over the past 100 years. In fact, it has been suggested that the gap between basic scientists and clinicians has increased over the past quarter century [4]. Among the reasons we have previously suggested is the organizational culture of academic medicine in which the ethos is the value of the discovery of new knowledge over all else and the relative merit of the ‘hard’ science of molecular biology as opposed to the ‘softer’ social sciences [3]. Moreover, basic scientists, who account for a large proportion of medical school full-time faculty, and clinicians tend to speak different languages or at least different dialects. The language of molecular biology, the lingua franca of academic medicine, has been very different from the language of patient safety and systems thinking, yet both talk about complex interdependent processes and activities in their work. The Rosetta stone, a tablet from the 2nd century BCE consists of three inscriptions that represent a single text. This parallel translation allowed the deciphering of Egyptian hieroglyphics. A Rosetta stone to translate between the languages of molecular biology and patient safety management could help faculty understand each other. Such communication could facilitate meaningful reform of the medical school curriculum to include patient safety management. In recent years there has been an increasing application of biological concepts to describe organizations as well as in system design [5–9]. We propose the outline of such a model to assist in bi-directional communication between these disciplines. We use the principles and mechanisms of the DNA damage response to describe the central concepts of safety science and discuss similarities and differences between the systems of DNA repair and organizational approaches to safety in health care.

Can cells teach us about health care organizations?

Parallels between organisms and organizations can be drawn from complex systems theory [5,10]. Tables 1 and 2 illustrate some of these parallels. A complex system is any system that
involves a number of elements, arranged in structure(s) that can exist on many scales (Table 1). Such a system is characterized by structures with interacting components, processes, and patterns of behavior or outcomes [11,12]. The interactions of the system’s components lead to an emergent phenomenon whereby the whole is greater than the sum of its parts; biochemical reactions are observed at the level of the cell whereas consciousness appears at the level of the organism. Non-linear behavior is also common; large interventions may have little effect while small changes may have large effects. Although there may be qualitative as well as quantitative differences as one moves along the hierarchy, there are also some striking similarities. Both DNA replication and health care delivery can be thought of as complex systems. Similarly the DNA damage sensing and repair system and the system for ensuring patient safety can be thought of as complex systems. They all have structures and processes to manage variability in order to ensure proper functioning and outcomes, although adverse outcomes may certainly occur (Table 2). This variability may be in input or output. Each has features to identify and reduce the variability in the input, features enabling the system to be resilient against residual variability, and finally, features enabling the system to learn from variability of the output. All of these actions must occur in the setting of considerable distraction or ‘noise’ [13].

### Noise

Genomic integrity must be maintained to ensure an organism’s (and species’) healthy survival. Genetic changes and the consequent synthesis of abnormal proteins or altered expression of normal proteins may cause cancer, premature aging, and inheritable disease. Maintaining this integrity must be done in the face of considerable external mutagenic load (e.g. environmental hazards—chemicals and UV and ionizing radiation). In addition, noise (stochastic fluctuation) is inherent in biochemical reactions [14,15]. More than 100 DNA
lesions occur in each mammalian cell daily from spontaneous decay and replication errors. To meet this challenge successfully, a series of enzymatic repair systems has evolved that sense the presence of DNA damage and transmit the signal to downstream effectors to either repair DNA damage or prevent the DNA damage from causing harm. It is a highly reliable system—risk, but safe and effective and its crucial importance is reflected in its early appearance in evolutionary development and conservation over time [16]. Stochastic fluctuation is inherent in organizations and they, like cells, are under constant threat from errors [17]. The frequency of errors is high. Many occur related to people, the technologies used, and the organization itself (e.g. policies and structure), but most often, errors occur as a result of the interactions among people, technology, and the organization [17,18]. In the case of an intensive care unit (ICU) this noise can be figurative (e.g. variability in the workload, use of complicated error-prone devices, and information overload) or literal (auditory alarms on ICU equipment) [19]. Yet, although not as robust as the so-called high reliability industries/organizations (commercial and military aviation and nuclear power) [20], health care organizations are robust in that they can manage and cure a variety of diseases despite the exposure to constant intrinsic and extrinsic noise. In one sense, both DNA replication and health care are fragile, i.e. very risky: a single mutation may be lethal and a single serious medical error can be lethal. Like the DNA damage response, patient safety is not so much a priority, but rather a precondition. How the highly reliable DNA damage response system manages the risk—deals with the variability in inputs, organizes the defenses, and learns from the outputs offers lessons for health care.

Variability in input

There are many different types (>100) of DNA damage including base damage and deletions, strand breakage, protein–DNA cross-links, and DNA–DNA cross-links (variability in input). There is also base mismatch that occurs during the normal replication process. Current models for DNA damage recognition include multiple types of sensors that detect characteristics specific to damaged DNA. Similarly, there are repair pathways for different types of damage. The DNA repair system is resilient/robust. Not only are the enzymes in the pathways inducible, they are redundant. The network of interacting repair systems and backup enzymes ensures that more than one repair system can correct the same defect [21]. The network structures, modular architectures, and layers of feedback regulation confer a higher degree of robustness [22–25].

Health care has high variability of input: the patient case mix, the nature and number of diseases as well as variation between different patients with regard to clinical manifestations and time of presentation. There is variability in the training and experience of health care staff, the effects of drugs, the design and function of technology, and in the way health care processes are organized. The complexity of health care also means that there are many different types of error. For example, a medication error could occur at any one of four stages: ordering, transcribing, preparation, or administration. Each of these stages is prone to different types of error. For example, an ordering error could relate to wrong choice of drug or wrong dose. As in the case of DNA damage response, there are repair pathways for different types of damage. There are multiple means for sensing damage. For example, decision support built into computerized physician order entry systems can identify drug incompatibilities, drug–drug interactions, anomalous dosing, or contraindications such as known allergy or decreased renal function [26]. One of the factors that account for the major reduction in deaths due to anesthetic administration was the development of pulse oximetry. This method permitted the detection of hypoxemia before it was manifest in either the patient turning blue or in the development of cardiac arrhythmia. A number of monitoring methods may be brought into play during anesthetic administration. These may include continuous electrocardiography, intermittent or continuous monitoring of blood pressure, and a variety of others. There is a network of interacting systems that includes the anesthesiologist himself or herself, providing a degree of redundancy. The specificity of replication enzymes has its parallel in the forcing function that makes it impossible to attach the nitrogen tank to the oxygen intake valve on an anesthesia machine. Reduction in input variability may be a driver in the development of specialized facilities that deal with relatively few conditions. This also allows for more focus on the processes involved.

Variability in processes/system

There are mechanisms to prevent the development of variability in the first place—defect prevention. There are systems that defend the organism against oxidative damage to DNA including the enzymic removal of reactive oxygen species, enzymic nucleotide pool sanitation (i.e. removal of damaged nucleotides to prevent them from being incorporated into DNA) as well as DNA repair. DNA polymerase is of high accuracy [27,28]. Moreover, as the DNA gets replicated and DNA polymerase adds new nucleotides to the growing DNA strand, it reduces the number of errors by removing incorrectly incorporated nucleotides with a proofreading function (inspection and quality assurance) [29]. DNA repair is closely integrated into cell cycle regulation, transcription, and replication through a system of checkpoint proteins [30]. When DNA damage cannot be repaired, the cell may respond by inducing transient cell cycle arrest or by inhibiting replication, transcription, and chromosome segregation causing cell death (apoptosis). This ensures that the damage will not be propagated further. At the same time, there are mechanisms to ensure that too much unnecessary apoptosis does not take place [20].

In health care there is variability in processes of care and in our attempts to diagnose and treat patients. Failure to follow protocol because of stress, lack of communication, or distractions are all examples of sharp-end errors that put the patients
at risk of injury. Further on there is understaffing, lack of routines regarding hand-offs, and outdated policies that become visible in frontline patient care but are caused by latent errors that come from the organizational or blunt end of the system [18,31]. The system of defenses in depth within the cell has its parallel in organizations. Organizations can cope with the risk of adverse events by creating layers of defense to prevent errors from propagating in the system and causing harm. These layers may be individual, team, institutional, or technical in nature. These layers may involve variability detection and feedback mechanisms, protective barriers that prevent errors from causing injuries, or any of a number of mechanisms. Because the layers of defense are multiple, multiple contributors (holes in the defenses) are required for any adverse event to occur. However, in contrast to the DNA repair system, most of the recovery actions in health care are dependent upon the people in the organizations who through heedfulness and quick adaptation to new situations play an important role in creating organizational resilience [20].

Variability in output and learning from that variability

Despite a highly evolved system for DNA repair, not all DNA damage is prevented or repaired. There are features that enable the organism to be resilient against this residual variability. Not all modification of DNA leads to mutation; not all base substitutions result in a change in the amino acid encoded by the RNA. Balancing the features of the system that ensure genomic integrity, e.g. the integration of the DNA damage response into cell cycle regulation, the system also ‘learns’ from its mistakes, i.e. learns from variability of the output. This accounts, in part, for the evolution of species better adapted to their environments. In a sense, this is a system that allows a certain amount of experimentation.

Studies published in many countries have shown that medical errors are common and that the consequences for patients and the health care system in general are enormous [1,32]. Cultural and legal barriers notwithstanding, there are many opportunities to learn from errors as well as near misses. High reliability organizations have been most successful in developing strategies for organizational learning from variability, e.g. having a good reporting culture (features that promote incident reporting, and feedback to the reporting community). When reported, lessons can be drawn and along with advances in science can serve as a starting point for continuous improvement both in the form of formalized organizational change and as more informal adaptation through change in work routines, in short, evolution.

Conclusions

We need to train physicians such that they are competent in a variety of areas such as diagnosis, treatment, and safety in order to provide excellent patient care. This will require not only the involvement of scientists of different, but equally legitimate disciplines, but also their active collaboration. Fortunately, these groups have more in common than might be readily apparent and each can learn from the other. Clearly, there are many major differences between cells and health care organizations. Types of behavior such as conscious action and learning occur in the latter, but not the former. Because the cells exist, we know that they can ‘afford’ the levels of redundancy in the DNA damage response that they possess. How much redundancy health care organizations can afford is an open question. However, cells and health care organizations share a variety of common features as well as problems they must manage. As in the preservation of genomic integrity, safety in organizations could be described as a dynamic non-event [20] where multiple safety strategies work together to create a dynamic equilibrium where the effects of errors are coped with constantly. These strategies must manage different sources of variability in the input, processes, and output of patient care. In contrast to the DNA damage response in which there is no conscious operator who is aware of the status of the system’s defenses, i.e. self-adaptation is an integral part of the system, high reliability organizations seek to interpose such a knowledgeable agent. Biological systems are remarkable for their high robustness, flexibility, and efficiency. We think that demonstrating the parallels between the DNA damage response and patient safety is one way to engage our molecular biology colleagues to facilitate getting patient safety management into the curriculum. Putting their teaching of molecular biology in a conceptual framework that allows for analogies to patient safety (and many other things) allows for reinforcement of principles at multiple levels of the curriculum. Although we do not expect molecular biologists to teach patient safety management, biomedical scientists possess a profound understanding of the complex mechanisms that govern organisms. Their insights may inform the design of safer health care systems. We suggest that such biomedical scientists can and should be engaged in the effort to bring education about patient safety management into the medical school curriculum and to make patient care safer.

References


Accepted for publication 6 March 2005