Journal of Biochemistry and Cell Biology

Review Article Open Access

A New Era in Toxicology Research: Systems Biology and Synthetic Biology Calreticulin's Biological Functions in Cancer

Yang Jinxi*

Angiogenesis Research Center, National Taiwan University, Taiwan

Abstract

Systems biology and synthetic biology are emerging disciplines that are increasingly being used in various areas of bioscience. Toxicology is starting to benefit from systems biology, and we believe it will benefit from synthetic biology in the future. As a result, a new epoch is on the horizon. This review demonstrates how a suite of novel techniques and tools can be used to better understand complex health and toxicology issues. We discuss the limitations of traditional computational approaches to toxicology and epidemiology research, using polycyclic aromatic hydrocarbons (PAHs) and their effects on adverse birth outcomes as an example. We discuss how systems toxicology (and its subdisciplines, genomic, proteomic, and metabolomic toxicology) can help to overcome such constraints. We specifically discuss the benefits and drawbacks of mathematical frameworks that computationally represent biological systems. Finally, we discuss the emerging discipline of synthetic biology and highlight relevant toxicologically focused applications of this technique, such as advancements in personalised medicine. We conclude this review by highlighting several opportunities and challenges that may shape the future of these rapidly evolving disciplines.

Calreticulin is an endoplasmic reticulum chaperone protein that is involved in a variety of cellular processes. It was discovered in 1974 to be a Ca2+-binding protein. Calreticulin appears to have a significant impact on the development of various cancers, and the effect of calreticulin on tumour formation and progression may vary depending on cell type and clinical stage. Calreticulin on the cell surface is thought to be a "eat-me" signal that promotes the immune system's phagocytic uptake of cancer cells. Furthermore, several studies show that manipulating calreticulin levels has a significant impact on cancer cell proliferation, angiogenesis, and differentiation. Aside from immunogenicity and tumorigenesis, interactions between calreticulin and integrins have been described during cell adhesion, which is an important process in cancer metastasis. Integrins are heterodimeric transmembrane receptors that connect the extracellular matrix to the intracellular cytoskeleton and initiate either inside-out or outside-in signalling. More and more evidence suggests that proteins binding to integrins may influence integrin-cytoskeleton interactions and thus cell adhesion ability. In this study, we reviewed the biological roles of calreticulin and summarised the potential mechanisms by which calreticulin regulates mRNA stability and thus contributes to cancer metastasis.

Keywords: Toxicology; Calreticulin; Extracellular; Endoplasmic Reticulum; Epidemiology

Introduction

Many areas of biological sciences and clinical medicine benefit from the application of the emerging disciplines of systems biology and synthetic biology. Toxicology research is no exception, and in recent years, toxicological procedures have begun to incorporate a wide range of computational techniques and artificial biological approaches for assessing the toxicological risk of chemicals. Historically, population-based studies of disease risk associated with environmental exposures relied on statistical associations for causal inference. The application of novel integrated approaches to toxicology investigations will improve our ability to distinguish causally relevant events between environmental exposures and disease outcomes [1]. Systems biology is one such approach.

The term "systems biology" refers to the study of the complex mechanisms underlying biological systems by treating the behaviour of genes, proteins, biochemical networks, and physiological responses as integrated parts of a larger system. As a result, the term "systems toxicology" was coined to describe the use of systems biology approaches in toxicological research. In practise, this method entails gathering large amounts of data from a variety of sources, including genomic, biochemical, proteomic, and metabolomic data [2]. This information is then used to inform computational models that can investigate the quantitative and qualitative behaviour of biological systems under a wide range of conditions. The primary benefit of this approach is the researcher's ability to model a wide range of complex biochemical events, many of which occur concurrently. This is in contrast to the reductionist approach of studying biological systems by focusing on a single small component that operates in isolation. Another approach that has the potential to change the face of toxicology is synthetic biology. It sits at the crossroads of several scientific disciplines, including chemical and electrical engineering, biology, bioengineering, and computational modelling. In fact, computational modelling is the glue that holds the fields of systems and synthetic biology together. Recent advances in this field have seen the creation of synthetic genetic circuits, gene promoters, proteins, and a wide range of synthetic biomolecules [3].

This review will provide a brief overview of some of the more traditional approaches to toxicological research before delving into recent developments in systems and synthetic biology that are relevant to toxicology research. The emerging face of toxicology research is systems biology and synthetic biology, which involve modelling

***Corresponding author:** Yang Jinxi, Angiogenesis Research Center, National Taiwan University, Taiwan E-mail: jixi_yang@neish.co.in

Received: 04-Jul-2022, Manuscript No: jbcb-22-71564, **Editor assigned:** 06-Jul-2022, PreQC No: jbcb-22-71564 (PQ), **Reviewed:** 20-Jul-2022, QC No: jbcb-22-71564, **Revised:** 22-Jul-2022, Manuscript No: jbcb-22-71564 (R), **Published:** 29-Jul-2022, DOI: 10.4172/jbcb.1000159

Citation: Jinxi Y (2022) A New Era in Toxicology Research: Systems Biology and Synthetic Biology Calreticulin's Biological Functions in Cancer. J Biochem Cell Biol, 5: 159.

toxicological effects with a mathematical framework and artificial cellular networks/tissues, respectively. The primary focus of this review is the role of computational modelling in the future of toxicology research. The rationale for this focus is that it is becoming increasingly important to integrate the massive amounts of data generated by systems toxicology into a coherent computational framework. We anticipate that such a framework will lead to a better understanding of how different toxicants interact with intracellular, physiological, and whole-body biological systems. This paradigm shift could reduce the number of animals used in toxicant risk assessment, enable illusory modelling of the effects of complex mixtures, create a template for individual toxicological exposure assessment based on age, gender, or genetic background, and improve risk assessment in the future [4].

Calreticulin (CRT) is a 46 KDa multifunctional protein found primarily in the endoplasmic reticulum (ER) and is highly conserved across species. It is made with a cleavable signal sequence at the N-terminus and an ER KDEL (Lys-Asp-Glu-Leu) retrieval signal at the C-terminus. CRT structural predictions revealed that the protein has three domains: N-domain, P-domain, and C-domain.

The CRT N-terminus is a globular domain with eight antiparallel -strands. This domain has the ability to interact with -integrins as well as the steroid receptor's DNA-binding site [5]. Calreticulin's disulfide bond formed by cysteine residues in the N-domain may interact with the P-domain to produce an important chaperone function.

There are two sets of three repetitive regions in the proline-rich P-domain. CRT's protein-folding function is mediated by these repeated amino acid sequences, which form lectin-like chaperone structures. Furthermore, the P-domain of CRT is a Ca2+-binding region with both high affinity and low capacity.

The C-domain of CRT is a highly acidic region that is important for Ca2+-buffering functions. It binds to Ca2+ with high capacity but low affinity. Ca2+ binding to this region is known to be important in ER chaperone protein interactions.

It is not surprising that this protein is highly enriched in the ER lumen because it contains a KDEL sequence for retrieval in the ER at the C-terminus of CRT. CRT is also found in the cytosol and on the cell surface, according to evidence [6]. The C-domain has been shown to be important for CRT retro translocation from the ER lumen to the cytosol. Further research indicates that ER Ca2+ depletion triggers this retro translocation process. Furthermore, some research has suggested that cytoplasmic CRT may interact with the cytoplasmic tail of -integrin via the KXGFFFKR sequences. Furthermore, cell surface CRT is linked to phagocytic uptake and immunogenicity. These findings support CRT's role as a multifunctional protein involved in a variety of physiological and pathological events in cells.

Traditional Approaches for Toxicant-Health Outcomes Research

Some of the older approaches to toxicology testing and risk assessment relied heavily on in vitro and in vivo experiments to generate data to assess health outcomes. Dose-response analysis studies are commonly used to investigate the biological effect of toxicants on a cell culture, an animal, or both over time. Negative biological responses can range from molecular and physiological perturbations to changes in behavior and even death. This method, however, has a flaw in that the response curve can change significantly when the species is changed. This is extremely crucial because the utility of any toxicological test is determined by its consistency and ability to determine the extent of the hazard associated with human exposure. There are issues not only with integrating data from different species for one contaminant, but also with integrating data from different chemicals in different species [7].

Toxicology studies involving mixtures frequently use statistical techniques to fit mathematical functions to toxicology data. Certain assumptions are underlying these statistical techniques. acrylamide concentrations in French fries and the associated life-time cancer risk were estimated using statistical nonlinear regression models. These methods are useful for detecting statistical associations; however, empirical models have limitations in that they do not account for toxicant-toxicant interactions. Furthermore, they do not account for the interaction of such chemicals with physiological or intracellular biological mechanisms, or how mechanisms are affected by toxicant levels. To tackle this problem, toxicology research makes use of a variety of mechanistic computational approaches. The well-established physiologically based pharmacokinetic/pharmacodynamic approach, for example, is capable of incorporating physiological mechanisms and predicting the change rate in chemical amount in tissues, chemical distribution, metabolic turn over, and toxicant excretion rate in a wide variety of animals, including humans; all of this information is encapsulated in the output from model simulations for a specific time course [8]. An intriguing recent application of PBPK modelling was to look into differences in cytochrome P450-mediated pharmacokinetics between Chinese and Caucasian populations. In both population groups, the model predicted plasma drug concentration-time profiles.

Single Exposures with Multiple Outcomes or Multiple Exposures and Single Outcome

One important translational aspect of toxicological research is its ability to inform risk assessment in order to improve human and environmental health. The empirical data generated, whether on a benchtop or on a laptop, is directly related to risk assessment. Current risk assessment strategies are informed by toxicity and exposure estimates, but they are limited by data gaps and areas of uncertainty. To deal with uncertainty, such as how chemical mixtures with similar structures or toxicity mechanisms interact, assumptions must be made. For example, two endocrine disrupters with similar chemical structures might be expected to have an additive effect on the endocrine system. Miller et al. discovered that coexposure to two endocrine disruptors, polychlorinated biphenyls and polybrominated diphenyl ethers, had additive effects. But only thyroid hormone reductions were included in that data set, which demonstrated an additivity that was presumptively true. Hypothyroidism also has complicated, frequently sex-specific neurological side effects.

The whole toxicological health effect of a mixture of toxicants may therefore be misunderstood if only one biological outcome in one sex is considered. We must use new, transparent approaches that are founded on unambiguous premises and a consistent mathematical framework that can be easily shared across disciplines if we are to effectively handle this complexity.

Toxicological impacts on populations must be predicted by determining whether complex chemical mixtures will have additive, synergistic, or antagonistic effects on biological processes. However, it continues to be one of the most challenging and frequently disregarded areas of toxicology for the simple reason that it is not time- nor cost-effective to conduct the necessary experimental settings to take into account every possible mixture of pollutants in various circumstances. Computational modelling may have a bright future in this case. Based on their chemical characteristics, which may be similar to those of already well-known chemicals, novel chemicals can potentially have effects that can be predicted.

Systems Level Thinking Is Needed in Population-Based Investigations of Health Outcomes

It is a complicated problem to extrapolate toxicological data to comprehend the impact on human health. First, due in part to the lack of information on chemical mixtures, there are limited tools to examine the consequences of exposure to toxicant mixtures on human health. Therefore, in vitro/in vivo toxicological equivalence factor is used to basis epidemiologic risk calculation of toxicant mixture exposure (TEF). This strategy presupposes that risks are additive and that they are equivalent across species. However, polycyclic aromatic hydrocarbons (PAHs), for example, can have synergistic or antagonistic effects depending on the individual PAH compound studied.

The second major multiscale and temporal challenge is the toxicant effects on many organ systems. PAHs have the potential to harm numerous organs. For instance, prenatal exposure to PAHs by maternal inhalation is linked to a variety of fetotoxic consequences, such as intrauterine growth restriction, preterm delivery, DNA damage, shorter height at age 3, and neurocognitive deficits in childhood. Additionally, some toxicological consequences don't become apparent until years after exposure. For instance, when a prenatally monitored group of babies was tracked until they reached school age, the prenatal PAH exposure further hampered neurodevelopmental abilities and raised the risk of symptoms related to asthma.

Thirdly, it has been discovered that some environmental toxins, notably a newly discovered class of endocrine-disrupting substances, have nonmonotonic dosage responses and low dose effects, especially when exposure occurs during infancy. Finally, the timing of the exposure during pregnancy affects how harmful it is. For instance, the brain is more negatively impacted by benzopyrene exposure in the first trimester, whereas the foetal liver is more susceptible to the toxin in the second trimester. Such temporal and tissue-specific concerns would be resolved by a systems biology-centered approach that would take into account how the toxicant affects the temporal behaviour of cells, tissues, and entire organ systems. With the help of this thorough investigation, the behaviour of a toxin can be predicted based on the species with which it is interacting. As a result, systems toxicology, which incorporates conventional methods within the paradigm of system biology, gives us a way to address some of the key problems in the discipline of toxicology. The processes underlying species-specific vulnerability to the neurotoxin 1,3,5-trinitroperhydro-1,3,5-triazine (RDX) were recently examined by Warner and colleagues using a systems toxicology approach. In zebrafish and fathead minnow fry exposed for 96 hours to RDX concentrations ranging from 0.9 to 27.7 mg/L in zebrafish, toxicity was measured using transcriptional, morphological, and behavioural markers. It was discovered that zebrafish and minnow fry had various degrees of sensitivity to this neurotoxin using this all-encompassing method. The systems toxicology paradigm was most recently successfully applied by Lu and colleagues (2014) when they combined traditional toxicology methods with transcriptomics and metabonomics to identify the processes underlying hepatic erythromycin estolate (EE) harm. An enhanced ATP-binding cassette (ABC) transporter, cell cycle, and p53 signalling pathway was found in differentially expressed genes in the livers of EE-treated rats, according to hepatic microarray analysis. Because of the toxicological effects of EE on the liver caused by oxidative stress, it has been shown using metabonomics research that exposure to EE can affect amino acid metabolism, lipid metabolism, and nucleotide metabolism.

Systems Toxicology: Recent Applications

Systems biology-centered techniques for toxicity research have been increasingly popular during the past few years. Such processes entail the application of so-called -omics techniques, such as transcriptomics, proteomics, and metabolomics. These methods produce a wealth of quantitative data by frequently using nuclear magnetic resonance, mass spectrometry, and microarray analysis. The management and archiving of this data is done using bioinformatics tools, and computational systems modelling then assembles mechanistic pathway models that can predict the behaviour of toxicity pathways both quantitatively and qualitatively using the data from these various sources.

Genomic Toxicology

In order to assess how the genome is controlled during transcription and replication in response to exposing a biological system to a harmful substance, toxicogenomics tries to employ global approaches. For instance, since DNA microarrays were first suggested as a tool to be utilised in toxicology research more than 15 years ago, the field of transcriptomics has been formed as a technology that may be employed in toxicological research. The area has advanced greatly in recent years, and numerous studies have looked at the levels of gene expression to ascertain the transcriptome reactions to toxicants. The transcriptome response of blood cells in employees exposed to the volatile chemicals toluene and trichloroethylene was investigated in a recent intriguing study by Song and colleagues. A distinct transcriptome signature that distinguished exposed participants from unexposed ones was determined through research, and 378 genetic markers were shown to be predictive of exposure to each of the toxicants.

With the development of new methodologies, system-wide research has changed; sequencing has altered the generation of data for genome-wide toxicity. RNA-seq has improved various toxicological studies that employed it to clarify the molecular consequences of crotonaldehyde exposure in macrophage-like cells, replacing microarrays that were previously used to construct expression profiles. 342 genes had significantly different expression levels in the first timepoint of the study, according to analysis of the transcriptome. Apoptosis, oxidative stress, immunological response, and inflammatory response pathways were among the gene categories impacted by crotonaldehyde exposure.

DNA can undergo epigenetic changes that affect its structure, expression, and inheritance as a result of exposure to environmental changes. For instance, DNA methylation can be brought on by a variety of toxins, both natural and man-made, and is seen throughout the genome by sequencing. To better understand how DNA methylation and asthma interact, MeDIP-seq was used to look at the methylome alterations in the lungs before and after exposure to environmental irritants. 213 genes were discovered to have differential methylation, 83 of which corresponded to the reference genome. Transforming growth factor beta signalling pathway was one of the epigenetically changed areas, showing a relationship between DNA methylation and asthma, according to further analysis of the 83 possibilities.

Metabolomic Toxicology (Toxicometabolomics)

Global metabolic profiling is a component of metabolomics. The broad range of metabolites that make up the metabolome are the subject of metabolomics. In contrast to proteomics and transcriptomics, metabolomics focuses on analysing small molecules, such as free fatty acids, amino acids, carbohydrates, and certain lipids, that are involved in metabolic activity. Toxicometabolomics is the term used to describe the use of metabolomics methods to toxicology. employed mouse metabolomics research to test the idea that two of trichloroethylene's metabolic byproducts were responsible for liver damage by triggering peroxisome proliferator-activated receptor, a crucial receptor involved

in fat metabolism. Due to decreased expression of PPAR target genes, TCE exposure reduced the levels of metabolites involved in fatty acid metabolism in urine.

The Exposome

Exposome theory is a concept that logically fits into the systems biology way of thinking. The exposome considers both the intrinsic and extrinsic chemical activities' harmful consequences. In this perspective, a biological system's internal environment is seen as a collection of chemical processes that have the potential to harm it, such as oxidative stress. This is in addition to external stressors like exposure to hazardous chemicals in the environment. From conception onward, the exposome contains both of these causes of biological harm. It is proposed that toxicant effects on a wide range of physiological health markers might be evaluated to provide an exposome profile over time.

Biological Functions of Calreticulin

CRT has been suggested in recent years to play a role in a number of physiological and pathological cellular processes. Protein chaperoning and Ca2+ homeostasis modulation are the two main tasks of CRT inside the ER. A growing body of research also shows that non-ER CRT controls vital biological processes such RNA stability, gene expression, and cell adhesion.

Protein Chaperone

For the production, folding, and transportation of secretory proteins, the ER is a crucial organelle. Molecular chaperones, which aid in proper protein folding and assembly, perform these tasks. For numerous proteins, CRT is one of the well-studied lectin-like ER chaperons. Recent research has shown that CRT, including integrins, surface receptors, and transporters, is engaged in the quality control process during protein synthesis.

Calcium Homeostasis

Ca2+ is a ubiquitous signalling molecule that primarily stores in the ER lumen and influences numerous cellular and developmental processes. Numerous studies suggested that Ca2+-binding chaperones affect the ER lumen's ability to store Ca2+. Due to the presence of two Ca2+-binding sites in both its P-domain (high-affinity, low-capacity) and C-domain, CRT is regarded as an intracellular Ca2+ regulator. More than 50% of the Ca2+ that is kept in the ER lumen is linked to CRT. Therefore, increased intracellular Ca2+ storage may result from higher levels of CRT. On the other hand, CRT-deficient cells have a reduced ability to store Ca2+ in the ER lumen. Mice lacking in CRT do not develop their hearts properly because CRT has a compromised ability to maintain Ca2+ homeostasis. Additionally, aberrant CRT function was linked to the adaptation of Henle's loop to osmotic stress and adipocyte differentiation. These results provide more evidence that CRT is essential for Ca2+ homeostasis.

Cell Adhesion

The idea that CRT might be involved in cell adhesion is based on the numerous processes through which focal contact is controlled. It is obvious that the molecules of the extracellular matrix (ECM) are crucial for the establishment of focal contacts. Studies have shown that changes in CRT levels have an impact on how cells adhere to different types of ECM, suggesting that CRT controls how sticky cells are via controlling fibronectin expression and matrix deposition. These effects are brought about by CRT's Ca2+-dependent influence on c-SRC activity. Additionally, prior research suggested that the direct contact between CRT and integrins through binding to the cytoplasmic KXGFFKR motif of the integrin -subunit may be the cause of CRT-mediated cell adhesion. These investigations offered proof that CRT is essential for maintaining cellular adhesiveness.

RNA Stability

AU-rich region in the 3′ -UTR is bound by an mRNA binding protein, which destabilises type I angiotensin II receptor mRNA. In addition, under situations of high glucose, CRT also binds to a particular region in the 3′ -UTR of the glucose transporter-1 mRNA, destabilising the mRNA.

These findings showed that CRT now has a new role as a trans-acting factor that controls mRNA stability.

Discussion

Systems biology has become increasingly prevalent in bioscience study over the past ten years. Those conducting toxicology research are beginning to notice its impact more and more in recent years. In order to provide an integrated interpretation and understanding of biological processes from the molecular to the systemic and to utilise these to assess disease risk, systems toxicology is an emerging field that aims to combine conventional toxicological methods with the systems biology paradigm. The general goals of this approach are to increase our knowledge of the mechanisms underlying toxicity, use dynamic computational models to forecast the toxicity of unidentified compounds or long-term effects of exposure, and use this emerging strategy to promote environmental protection and public health for the benefit of society. Recent worthwhile instances of how applying this integrative approach to investigating biological systems has helped toxicant studies are numerous. As a result, the terms "systems toxicology" and the "toxicogenomics," "toxicoproteomics," and "toxicometabolomics" subdisciplines with an omic focus were coined. These methods have recently been used widely in toxicology research, in everything from studies that identified specific transcriptomic profiles to exposure to volatile chemicals to studies that used metabolomic profiling to look at in vivo plasma responses to dioxin-associated dietary contaminant exposure in rodents. Until now, computational systems biology has possibly received the least attention. The BioModels database, a repository for models housed in SBML, the primary exchange format for systems biology, currently has a dearth of computer models with toxicology themes. This is significant because mathematical modelling has historically been utilised in toxicology investigations to determine the potential health risks of toxicant exposure. It is also surprising that some modelling techniques that are frequently employed in systems biology, such as stochastic intracellular modelling, have not been studied more extensively in toxicity research. As a starting point for the construction of a thorough mechanistic computational model, we are now leveraging our previously published work that explored the effect of PCBs and PDBEs on T4 levels in rodents.

His review also identified numerous instances of how synthetic biology, a young field whose objective is to develop and put together innovative synthetic biological entities, is starting to have an impact on toxicological research. By designing and engineering unique bacterial organisms that express genes capable of digesting dangerous compounds like the herbicide atrazine, it is evident that this new discipline has being used to further toxicological research. In terms of the potential use of synthetic biology in toxicology research, we propose an ambitious project that encourages the creation of a synthetic liver that can replicate the effects of glucuronidation. The creation of such a synthetic construct has a number of obvious advantages and gains, such as a decrease in the quantity of rats employed in toxicological

studies and a decrease in the expense of these research projects. But before it can be completed, this initiative must go through a variety of restrictions and challenges. For example, it would be essential to deepen our understanding of the biological processes underlying glucuronidation. Additionally, it would be important to expand our understanding of how toxicant-toxicant interactions affect how the route behaves. Such a technology would have enormous potential and surely influence how toxicant investigations are carried out in the future.

Conclusion

We outlined the supporting data for CRT's influence on the emergence of cancer in this review. Notably, bad outcomes in several cancer types are substantially linked with aberrant CRT levels. Numerous studies have demonstrated that CRT takes part in a variety of cellular processes both inside and outside of the ER lumen. Protein chaperoning and Ca2+ homeostasis are the two main roles of CRT, however growing data suggests that non-ER CRT also plays a critical part in tumour growth. Interaction with integrins is one of the significant CRT-mediated mechanisms that controlled cancer cell adherence. A variety of integrin cytoplasmic-binding proteins are affected by integrin activation, which affects cytoskeletal dynamics in addition to linking to extracellular matrix. Since FUT1 levels affect integrin glycosylation, CRT has gained recognition as an integrin -subunit binding protein that can aid in 1-integrin activation. It will be vital to comprehend how CRT controls cell adhesion in light of this. How CRT levels were raised in various cancers remained a mystery. Future research should be necessary to identify the potential upstream signal of CRT-related cancer progression, and these findings will clarify the functions of CRT in the biology of cancer.

There are several restrictions on systems and synthetic biology. The extent to which these problems are resolved will determine how well these new fields continue to be integrated with toxicology research. The calibration of computational models is one of systems biology's main present limitations. This has important ramifications for toxicological research because risk assessment is crucial and highly sensitive models limit their potential utility. However, it is expected that mechanistic computational systems modelling will be used more frequently once tools for inference, such as Bayesian computational methods, and optimization are used to calibrate systems models. It's a good thing that recent initiatives have centred on overcoming this important computational systems modelling constraint. Personalized medicine is a keyword that is worth examining if one thinks about the potential future chances for these fields, and one might accept that personalised toxicology has comparable implications. Systems biology, however, offers the possibility of individualised toxicology. Think about, for instance, how modifying a model to reflect the various CYP enzyme activity for drug metabolism, in addition to age-related changes in enzyme activity, may be easily accomplished. In such a case, it would be able to forecast the consequences of toxicological exposure on not only a certain group but also on a single person, turning enormous datasets into simulations that are specific to the individual. The fact that no synthetic structure has yet been created that is sufficiently biologically accurate to depict how a toxicant or combination of toxicants might interact with a whole organ system is a significant limitation of synthetic biology from a toxicology perspective. There is a need for an innovative method of measuring the toxicity of synthetic and natural substances on organ and systemic levels. The synthesis of synthetic genetic components has limitations as well because it is frequently a time-consuming procedure.

Acknowledgments

The author would like to acknowledge his Angiogenesis Research Center, National Taiwan University, Taiwan for their support during this work.

Conflict of Interest

The author has no known conflicts of interested associated with this paper.

References

1. Majeti R (2009) CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. Cell 138: 286-299.
2. Feng M (2015) Macrophages eat cancer cells using their own calreticulin as a guide: roles of TLR and Btk. Proc Natl Acad Sci USA 112: 2145-2150.
3. Lagasse E, Weissman I L (1994) bcl-2 inhibits apoptosis of neutrophils but not their engulfment by macrophages. J Exp Med 179: 1047-1052.
4. Chao MP (2011) Therapeutic antibody targeting of CD47 eliminates human acute lymphoblastic leukemia. Cancer Res 71: 1374-1384.
5. Denning DP, Hatch V, Horvitz HR (2012) Programmed elimination of cells by caspase-independent cell extrusion in C. elegans. Nature 488: 226-230.
6. Johnsen HL, Horvitz HR (2016) Both the apoptotic suicide pathway and phagocytosis are required for a programmed cell death in Caenorhabditis elegans. BMC Biol 14: 39-56.
7. Lauzon RJ, Rinkevich B, Patton CW, Weissman IL (2000) A morphological study of nonrandom senescence in a colonial urochordate. Biol Bull 198: 367-378.
8. Lauzon RJ, Patton CW, Weissman IL (1993) A morphological and immunohistochemical study of programmed cell death in Botryllus schlosseri (Tunicata, Ascidiacea) Cell Tissue Res 272: 115-127.