PERSPECTIVE

In a growing bio economy, biotechnology may be used to create secure biocontainment designs

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ABSTRACT

GMOs have become an important part of a sustainable bio economy, with a wide range of uses in agriculture, bioenergy, and healthcare. The fast growth of GMOs and allied synthetic biology technologies, on the other hand, presents a variety of biosecurity issues about GMO environmental escape, detection, and effect on native ecosystems. From traditional auxotrophies to global genome recoding, a variety of genetic protections have been implemented in a variety of microbial hosts. However, a greater knowledge of the basic principles driving microbial responsiveness to biocontainment limitations and GMO interaction with the environment is necessary to achieve the full potential of microorganisms as bio catalytic platforms in the bio economy. We examine current analytical biotechnological advancements and methodologies for assessing biocontainment and microbial bio productivity, as well as prospects for predictive systems bio designs to ensure a successful bio economy, in this paper.

Key Words: *Genetically Modified Organism (GMOs); Bio contaminants*

INTRODUCTION

Concerns about transgenic organism escape and the possibility of transgenic DNA being exchanged with native species in the ecosystem demand very effective biocontainment measures. To date, a number of synthetic biology-mediated biocontainment strategies have been developed, with varying degrees of efficacy. These strategies primarily rely on: (I) metabolic auxotrophy, (ii) inducible control of systems detrimental to cell health, and (iii) rewriting the genetic code using xenobiological and/or synthetic coding components. Many have successfully met or exceeded the National Institutes of Health's (NIH) criterion, which states that a GMO escape rate of less than 1 in 108 cells is deemed to be acceptable safe. However, there are still a lot of unanswered problems about GMO stability, resistance, escape frequency, and performance and containment at scale and under varying environmental circumstances. The principles controlling biocontainment, as well as the influence of genetic protections on microbial fitness and bio productivity in industrial hosts, are yet unknown. Combinatorial methods to include several genetic protection schemes have produced surprising outcomes, highlighting the knowledgebase gap. Furthermore, these techniques have mostly been tested in model microbial systems (e.g., E. coli); their applicability to non-model, industrial production hosts are unknown. We explore future potential for attaining predictive control of secure, high-productivity bio designs and examine current methodologies for studying biocontainment in microbial systems.

Engineered auxotrophies, or the genetic knockout of a gene involved in the manufacture of an essential metabolite, were used in the first documented microbial biocontainment techniques. Though generally effective in the laboratory for selection and biocontainment, with escape frequencies of less than 10-13, such approaches tend to fail outside of strict laboratory conditions, as these essential metabolites can be scavenged from the natural environment, such as soil, water, and native microbes. The possibility of intra-species or inter-species Horizontal Gene Transfer (HGT), which allows for the reacquisition of critical genes, further jeopardizes auxotrophic confinement. The difference in escape frequencies between a lab and a natural setting emphasizes the need of simulating natural circumstances when evaluating biocontainment measures. Another method of biocontainment is to conditionally express proteins that are harmful to cells. Membrane destabilizing proteins, for example, can be regulated by a tiny chemical that represses the expression of the hazardous gene, such that if the organism escapes into nature, the lack of the repressor results in toxic gene expression and cell death. To combat the risk of HGT, scientists used nucleases as a kill switch, which kills cells by destroying their DNA; once damaged, native and transgenic DNA is no longer available for transfer to wild type species. Additional toxin-antitoxin matching methods have also been found to be successful. More recent research on kill switches has focused on multi-layer, programmable control, such as the construction of a logic gate in which cell survival is dependent on the input of two tiny molecules and the lack of a third. The relative ease with which cells may change their DNA and therefore escape biocontainment is a noteworthy disadvantage of simple kill switches, which might be alleviated by tactics that minimize host mutation rates or the use of redundant devices.

While significant progress has been achieved in the creation of new biocontainment measures, the analytical approaches used to evaluate their effectiveness have largely remained unaltered. In the majority of biocontainment investigations to date, growth in liquid medium or on agar plates has been utilized to estimate the risk of escape. Although valuable for establishing a baseline of effectiveness, medium and plate-based tests have significant disadvantages and limitations. These assays are meant to examine single strategy quantitatively at a time, but they are not capable of analyzing many combinations at the same time. Furthermore, plate tests may miss temporary resistance. More crucially, these trials fail to account for the complexities of an environmental release, as well as the possible implications of industrial-scale growth on biocontainment module efficacy. The use of combinatorial biocontainment libraries and pooled screening methodologies to measure both bio productivity and biocontainment stability should speed up high-throughput screening of biocontainment modules. Recent improvements in DNA barcoding technologies, which provide an effective way to track biocontainment designs in combinatorial space, might complement such techniques. Mesocosm studies have long been used to assess environmental perturbations such as pathogen survival, gene flow between transgenic and native organisms, phenotyping genetically modified microbes, and pollutant impacts as a stop-gap between lab-based evaluations and in situ deployment. Mesocosms are well suited not only to investigate the stability of a biocontainment module in a realistic escape scenario, but also to provide insights into the potential impacts of release other than propagation, such as HGT or metabolic shifts in a multitrophic environment, because they mimic environmental conditions.

Recent breakthroughs in computer modelling have provided a way to contextualize multi-omic data in order to relate genotypes to phenotypes, laying the groundwork for predictive design and control. Genome-scale Metabolic Models (GEMs), for example, have developed as a strong tool for defining an organism's full metabolic potential, offering a global picture of its metabolism and gene–protein(enzyme)–reaction–metabolite links. Flux balance analysis, a linear programming optimization approach, is used to solve GEMs, and biomass generation is commonly utilized as an objective

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function as a surrogate for growth. The use of processes across metabolic networks is predicted in this optimization procedure to obtain a maximum or lowest flow of the goal function. GEMs are thus a useful tool for identifying biocontainment gene targets as well as metabolic targets for bio production optimization. Integrated metabolic and gene expression models (ME-models) are a type of GEM that calculates the molecular makeup of cells as a function of genetic and environmental characteristics. Experimentally collected multi-omics data may be analyzed within a complete modelling framework using the ME-model, which directly predicts transcription and protein abundances. The ME-model isn't just for metabolism; it can also reliably predict protein synthesis, metal utilization, and translation effectors. Importantly, all components of these processes' energy costs are represented, which can help educate bio production optimization in the context of biocontainment limitations.

Recent improvements have increased computer power, allowing for the creation of genome-scale models for co-cultures and communities, making it easier to study symbiotic relationships and interactions in microbial systems. Community modelling techniques like these have been used to anticipate networks of connections including syntrophic metabolite transfers and community assembly factors. Determining carbon metabolism in changing contexts requires an understanding of these dynamic dynamics. These studies have also been used to see if genetic mutations, which are generally fatal in axenic cultures, may be saved in co-culture. For fail-safe strain designs, accounting for all conceivable ways GMOs could survive otherwise fatal perturbations in a community environment would be crucial. State-of-the-art metabolic robustness analysis can also help bio-secure designs. This method provides a one-of-a-kind capability for predicting and evaluating the fitness of a dynamic biological system, particularly when the system behaves differently in laboratory and wild settings. When a laboratory effector stabilizes the action of a critical enzyme in a modelled biocontainment circuit, the GMO microorganism will demonstrate steady-state metabolism. The targeted enzyme will be down regulated in an uncontrolled environment when the effector is missing, depleting the pool of a critical metabolite(s) and resulting in GMO instability during escape. Ensemble modelling may be used to deploy metabolic resilience in the context of biocontainment modules, where a series of models with varied kinetic data are parameterized and disturbed by altering maximum rate, which is largely proportional to the enzyme's control level. This method calculates the likelihood of system failure for each perturbation. Such methods can eventually be used to identify novel metabolic targets for bio-secure design, as well as evaluate the survivability of a modified laboratory organism in response to environmental changes.

CONCLUSION

The development and deployment of biocontainment solutions that are as secure at industrial scale and under environmental circumstances as they are on the benchtop, without losing the productive ability of GMO strains, is critical to the promise of a sustainable and prosperous bio economy. As a result of the systems level analysis mentioned above, critical regulatory networks that are differently regulated in response to genetic protections and subsequent environmental escape will be identified. Large-scale deployment and simulated environmental release using mesocosms will enable for thorough testing of biocontainment modules as well as information on the resilience and fitness of created bacteria. Robustness analyses and GEM will make it easier to integrate multi-omic and phenotypic data, as well as give a framework for designing biocontainment modules rationally. The fundamental processes that determine the efficacy of biocontainment and metabolic fitness will be elucidated as a result of these efforts. The knowledgebase that emerges will serve as a template for predictive design and provide the groundwork for future biocatalysts, paving the road for a sustainable bio economy.