CellPress

NCI-DREAM Project, XNAzymes, and Galactolipids in Plant Resistance

Each month, *Chemistry & Biology* Select highlights a selection of research reports from the recent literature. These highlights are a snapshot of interesting research done across the field of chemical biology. This month's Select highlights a community-driven effort to improve drug sensitivity prediction algorithms, a report that XNAs can act as catalysts, and the role of galactolipids in systemic acquired resistance in plants.

Community with Big DREAMs

The image illustrates the global nature of the efforts that went into the NCI-DREAM project to assess performance of drug sensitivity prediction algorithms. The circles represent the location of the research groups that submitted their methods for the assessment. Image courtesy of the NCI-DREAM Challenge organizers.

One of the most remarkable developments in biomedicine over the last decade is the dramatic increase in speed and reduction in cost at which we can generate large amounts of genomic, epigenomic, and proteomic information. For example, the cost of whole genome sequencing is now at the level of a few thousand dollars per genome, making genome sequencing for routine clinical applications close to reality. The combined use of genomic, epigenomic, and proteomic information for individual patients enables the application of precision medicine approaches and tailored treatment options to fit each patient's unique situation and circumstances.

Before precision medicine becomes a clinical norm, however, there is a need to develop better understanding of how to use the large amounts of data coming out of these analyses to predict how a given drug will perform given the genomic context of a patient. Development of drug sensitivity prediction algorithms is an active field of research aimed at addressing this need. Recently, the National Cancer Institute and the Dialogue on Reverse Engineering Assessment and Methods (DREAM) project came together to provide unbiased analysis and assessment of 44 drug sensitivity prediction algorithms. The effort lasted 5 months and involved 127 researchers across the globe. Each group behind the 44 algorithms was provided with access to DNA copy number variation, transcript expression, mutations, DNA methylation, and protein abundance data for 53 breast cancer cell lines. They were also provided with dose-response data to 28 drugs for 35 of these cells lines and asked to predict how the remaining 18 cells lines will respond to the same group of compounds. The methods were ranked based on how well they performed in predicting drug sensitivity for all cell lines and compounds tested. Some general observations about the performance of these methods are that modeling nonlinearities in the data in general improves the performance, as does including learning weights for the input data, and prior knowledge, such as information about biological pathways. It is exciting to see the community coming together in this way and generating a valuable resource for further development of computational approaches for predicting drug sensitivity.

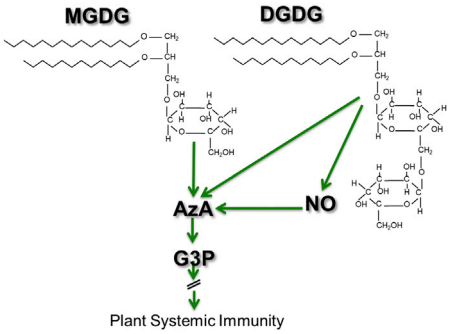
Costello et al. (2014). Nat. Biotechnol. Published online June 1, 2014. http://dx.doi.org/10.1038/nbt.2877.

Introducing XNAzymes

In the world of nucleic acids, the precedent that both DNA and RNA can serve not only to store and transmit genetic information but to catalyze chemical transformations has been well established. Catalytic RNA and DNA molecules, known as RNAzymes and DNAzymes, respectively, can facilitate a number of different reactions and can be evolved to acquire new functions. Although RNAzymes exist in nature, all DNAzymes reported so far have been man made. Nonetheless, both classes of nucleic acid enzymes are of practical technological interest and of more fundamental interest to enzymologists and those working on questions related to origin of life.

Xeno nucleic acids, XNAs, are synthetic genetic polymers in which ribose and deoxyribose that form RNA and DNA backbones, respectively, are replaced by other types of linkages. This results in molecules that are able to store information, evolve under laboratory conditions, fold into well-defined structures, and bind ligands, making them very similar to naturally occurring DNAs and RNAs. However, whether XNAs can catalyze reactions has not been previously reported. Taylor et al. now report that XNAs, made of four different scaffolds with arabinose (ANA), fluoro-arabinose (FANA), cyclohexenol (CeNA), or 1,5-anhydrohexitol (HNA) in the backbone, are enzymes that perform functions of RNA endonuclease, RNA ligase, and XNA ligase. Some of the XNAzymes described have rates of reaction close to that seen in DNAzymes and RNAzymes, but some are not as active and their reactions are significantly slower, albeit faster than when no catalyst is

used. The authors offer an intriguing explanation for this effect: what if these ''slower'' XNAzymes are more catalytically active under nonphysiological conditions and thus might be important for supporting the emergence of life under extraterrestrial and/or prebiotic conditions. A provocative thought, indeed!
Taylor et al. (2014) Nature. Published online December 1, 2014. http://dx.doi.org/10.1038/nature13982.



New research shows that monogalactosyldiacylglycerol (MGDG) and digalactosyldiacylglycerol (DGDG) play a role in plant systemic immunity. MGDG and DGDG were found to have different roles and affect levels of different signaling molecules involved in mediating the systemic immune response. Image courtesy of Pradeep and Aardra Kachroo.

Why Plants Arm Themselves with Galactolipids

As well as being a mouthful to pronounce, monogalactosyldiacylglycerol (MGDG) and digalactosyldiacylglycerol (DGDG) are plant galactolipids especially abundant in chloroplast membranes. Humans care about them because they are to a great extent responsible, due to their anti-inflammatory and anticancer activities, for the claim that green leafy vegetables are one of the healthiest food choices. The reasons why plants invest in producing large quantities of MGDG and DGDG have to do with the specific physicochemical properties that their presence imparts on the membranes in which they are found. But that's not where their roles end, as galactolipids have been associated with systemic acquired resistance (SAR), a process in plants that plays a role analogous to the innate immune system in animals; however, the mechanistic details have not been well established.

In their recent work, Gao and colleagues explore the biochemical basis for the link between the two galactolipids, MGDG and DGDG, and SAR using wild type and transgenic plants in which production of MGDG and DGDG was interrupted by mutating enzymes critical for MGDG and DGDG biosynthesis, respectively. The authors present evidence that the two galactolipids have nonredundant roles in regulating SAR, as they contribute at different steps in the SAR process. MGDG is found to function through regulation of a plant's ability to produce two components of the SAR signaling arsenal: glycerol-3-phosphate (G3P) and azelaic acid (AzA). On the other hand, DGDG seems to be directly linked to early SAR steps and the levels of two other signaling molecules, nitric oxide (NO) and salycilic acid (SA). Digging even deeper, Gao et al. show that a feature of DGDG that is essential for normal SAR function is the axial hydroxyl group at C4 of DGDG galactose. Overall, SAR is a complex process that involves multiple signaling pathways, signaling molecules, and now galactolipids.
Gao et al. (2014) Cell Rep. Published online November 26, 2014. http://dx.doi.org/10.1016/j.celrep.2014.10.069.

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