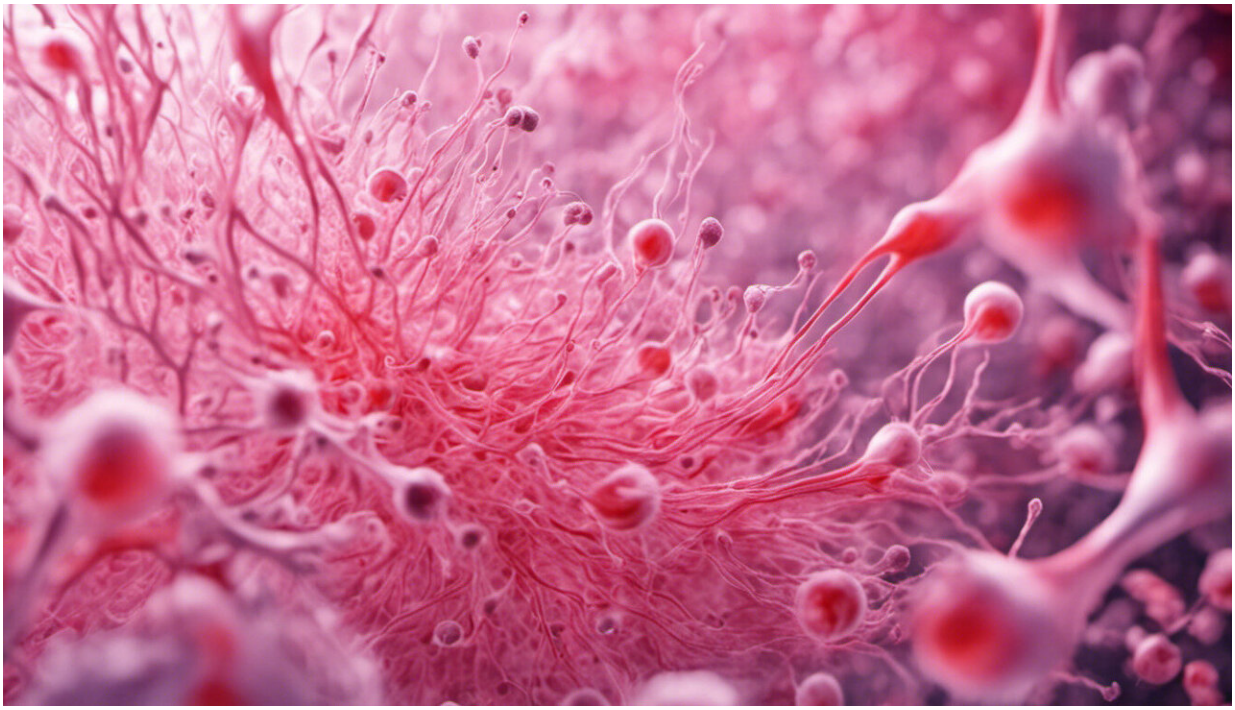
Accelerating cellular assembly lines

January 2 2013



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The immune system generates antibodies to mark threats that need to be eliminated, and these protein complexes bind their targets with remarkable strength and selectivity. Scientists have learned how to generate cell lines that can produce large quantities of specific 'monoclonal' antibodies (mAbs) with desirable properties; these mAbs are powerful tools for diagnostics, medicine and biological research.

The selection of suitable cell lines is an important aspect of large-scale production, as these can vary considerably in their individual mAb output. To assist manufacturing facilities in maximizing the generation of these precious molecules, Ying Swan Ho's team at the A*STAR Bioprocessing Technology Institute in Singapore has identified key features of top-performing cells in mAb-producing cultures.

Previous efforts have sought genetic differences that might affect production, but Ho and co-workers instead devised a strategy that allowed them to directly compare levels of metabolically active molecules present in Chinese hamster ovary (CHO) cells that secrete large or small amounts of a given mAb. "This approach enabled us to gain a deeper insight into the metabolic milieu that supports recombinant protein production in mammalian cell cultures," explains Ho.

The researchers cultivated CHO clones that were either high or low mAb producers, where productivity differed by up to 28-fold. They observed clear differences between the two groups in levels of molecules associated with several key metabolic pathways. For example, high-producer clones contained elevated levels of compounds associated with the electron transport chain, a mechanism that generates the adenosine triphosphate (ATP) molecules that power virtually every cellular process.

As energy and mAb production ramp up, cells also generate large quantities of molecules known as reactive oxygen species, which can inflict serious damage on the cell. This threat can be neutralized by molecules such as reduced glutathione (GSH). Ho and co-workers determined that high producers of mAbs also generated greater amounts of GSH than their low-production counterparts.

These findings offer a more global view into how CHO cells might brace themselves to handle the rigors of large-scale protein synthesis. The researchers now intend to explore the individual contributions of these

various metabolic pathways. "This will be done by evaluating the effects of increasing the cellular pools of these metabolites on mAb productivity in different cell lines," says Ho. With a deeper understanding of the key pathways, scientists should be able to either improve the selection of mAb-producing clones or modify culture conditions to ensure that the cells can work as hard as possible.

More information: Chong, W. P. K., Thng, S. H., Hiu, A. P., Lee, D.-Y., Chan, E. C. Y. & Ho, Y. S. LC-MS-based metabolic characterization of high monoclonal antibody-producing Chinese hamster ovary cells. *Biotechnology and Bioengineering* 109, 3103–3111 (2012). onlinelibrary.wiley.com/doi/10 … 2/bit.24580/abstract

Provided by Agency for Science, Technology and Research (A*STAR), Singapore