is a problem. *P. pichia* can produce very high concentrations of proteins, but the use of methanol presents challenges in reactor control and safety. *Bacillus* and the lower fungi may have well-developed secretion systems that would be attractive if they can be harnessed. Animal cell culture is required when posttranslational modifications are essential. Mammalian cells offer the highest degree of fidelity to the authentic natural product. Insect cell systems potentially offer high expression levels and greater safety than mammalian cells at the cost of a potential decrease in the fidelity of posttranslational processing. Transgenic animals are good alternatives for complex proteins requiring extensive posttranslational processing. Transgenic plants and plant cell cultures are emerging as production systems for high-volume protein products. Plants are well suited to produce proteins for oral or topical delivery.

A host–vector system is useful only if it can persist long enough to make commercially important product quantities. *Genetic instability* is the loss of the genetic information to make the target protein. *Segregational instability* arises when a plasmid-free cell is formed during cell division. *Structured instability* results when the cell loses the capacity to make the target protein in significant quantities due to changes in plasmid structure. *Host-cell derived instability* occurs when chromosomal mutations decrease effective plasmid-encoded protein production while the cell retains the plasmid. *Growth-rate-dependent instability* is a function of the growth-rate differential between plasmid-free and plasmid-containing cells; it is usually a determining factor in deciding how long a fermentation can be usefully maintained. Simple models to evaluate genetic instability are available.

The vector must be designed to optimize a desired process. Factors to be considered include vector copy number, promoter strength and regulation, the use of fusion proteins, signal sequences and secretion, genes providing selective pressure, and elements enhancing the accuracy of vector partitioning.

The engineer must be aware of the regulatory constraints on the release of cells with recombinant DNA. These are particularly relevant in plant design, where guidelines for physical containment must be met. Deliberate release of genetically modified cells is possible, but extensive documentation will be required.

Two increasingly important applications of genetic engineering are metabolic or pathway engineering for the production or destruction of nonproteins and protein engineering for the production of novel or specifically modified proteins.

SUGGESTIONS FOR FURTHER READING

Overviews on genetic engineering for protein production

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