INSECT CELLS AS A PRODUCTION PLATFORM FOR BIOPHARMACEUTICALS

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Introduction. *In vitro* cultured insect cells (IC) and particularly lepidopteran cells are an attractive alternative to mammalian cells for biomanufacturing. The coupling of IC culture with the lytic capacity of baculovirus expression vector systems (BEVS) constitutes the IC-BEVS production platform for the abundant and versatile formation of heterologous gene products, including proteins, vaccines and vectors for gene therapy. This presentation summarizes current knowledge on insect cell metabolism, culture conditions and applications of their infection with recombinant vectors.

Methods. Unlike many industrial mammalian cell culture systems, the IC-BEVS platform is based primarily on engineering the vector and not the host cell line. This shortens drastically the time from gene cloning to protein overproduction. The most prominent IC lines are those derived from the Lepidoptera *Spodoptera frugiperda* and *Trichoplusia ni* whose high susceptibility to infection by *Autographa californica* multiple nucleopolyhedrosis virus (AcMNPV) has prompted the use of the latter for vector construction in the IC-BEVS. Recombinant baculovirus vectors (r-BV) are constructed typically, but not exclusively, by the replacement of the polyhedrin gene (*polh*) by a foreign gene controlled by the strong late *polh* promoter. This allows the production of recombinant protein at very high yield following the lysis of the host IC after infection with the r-BV.

Results. Heterologous gene products such as proteins, vaccines and vectors for gene therapy can now be manufactured on a large scale thanks to the development of efficient and scalable production processes involving the integration of a cell growth stage and a stage of cell infection with the r-BV. Insect cells can be used to produce multimeric proteins functionally equivalent to the natural ones and engineered vectors can be used for efficient expression. The IC-BEVS system is also ideal for the production of virus-like particles as a new generation of cost-effective and safe vaccines. IC can be cultivated easily in serum- and protein-free media (Agathos, 2007). Having displayed its success in the production of safe biopesticides in previous decades, the IC-BEVS system is progressively adopted by the biotechnology industry and many products are today in clinical trials and on the market for veterinary and human applications both in prophylaxis (vaccines) and therapy. In addition to the versatility displayed in the construction of recombinant vectors (Summers, 2006) major advances have been made in the understanding of the physiology of IC in culture, leading to the development of robust bioreactor-based process sequences of growth and infection (Ikonomou et al, 2003; Agathos, 2010; Drugmand et al, 2012).

Conclusions. Although its most recognized applications have been primarily in the production of ecologically safe viral pesticides and of recombinant proteins in the research and diagnostics sector, the IC-BEVS platform is experiencing renewed interest for new applications in human and animal health, including biopharmaceuticals and new-generation vaccines. Cultured insect cells are also well-positioned for the production of viral vectors for cell therapy and for the efficient expression of multimeric or otherwise unwieldy proteins of interest in fundamental biological research or in drug discovery, sustainable agriculture practice, etc. The in-depth understanding of both uninfected and infected insect cell physiology using metabolic engineering and the constant improvement of insect cell media and culture techniques are bound to contribute to the rational design and validation of robust, scalable, and safe production processes based on the IC-BEVS technology.

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