METABOLIC DRIVERS OF IC-BEVS PRODUCTIVITY: TACKLING THE PRODUCTION OF ENVELOPED VIRAL PARTICLES

Francisca Monteiro, iBET, Oeiras, Portugal; Instituto de Tecnologia Química e Biológica, Universidade Nova de Lisboa, Oeiras, Portugal
fmonteiro@itqb.unl.pt

Vicente Bernal, Universidad de Murcia, Murcia, Spain; Current address: Centro de Tecnología de REPSOL, Móstoles-Madrid, Spain

Paula M. Alves, iBET, Oeiras, Portugal; Instituto de Tecnologia Química e Biológica, Universidade Nova de Lisboa, Oeiras, Portugal

Key Words: Baculovirus expression vector system; insect cells; metabolic flux analysis; metabolomics; bioprocess optimization; influenza VLPs.

The Insect Cell-Baculovirus Expression System (IC-BEVS) has a major track record for the production of recombinant proteins and vaccines. Although its widespread use, the physiological aspects that contribute to systems productivity are still to be fully disclosed.

In the present work, the metabolic features of the two main insect host cell lines, Sf9 and High Five, were analyzed during cellular growth and after baculovirus infection for the production of enveloped Influenza VLPs (Inf-VLPs). The gathered data were contextualized in a metabolic network representative of central carbon and nitrogen metabolism. Metabolic Flux Analysis (MFA) was performed to have a quantitative overview of the cellular fluxome dynamics that followed infection. In addition, the main carbon sources that contributed most to flux activity were identified. The impact of baculovirus infection on the physiology of High Five and Sf9 host cell lines was assessed by metabolomics, aiming at the identification of metabolic markers of productivity. The information herein generated was used to design tailored supplementation schemes that could boost IC-BEVS production yields of two enveloped viral particles: influenza VLPs (Inf-VLP) as a vaccine candidate and the recombinant baculovirus (BV).

The strong correlation observed between the metabolic state of the host cell and baculovirus infection highlights the capacity of this virus to act as a metabolic engineer, re-directing the cellular fluxome to support virus replication and production. The results also show that the viral load influence the cellular responsiveness to the supplements, with lower MOIs retrieving higher improvements in specific productivity. The careful selection of the MOI, along with the supplementation of culture medium with compounds altering cellular redox state and cholesterol metabolism, yielded a 6-fold improvement of specific productivity. These results pave the way to deepen our knowledge on the relationship between host cell and virus, contributing to the disclosure of the metabolic determinants that contribute to productivity.