

ABSTRACT

Cancers represent a group of unprecedented heterogeneous diseases and currently available anti-cancer therapies provide highly variable efficacy with unsatisfactory cure rates. A wide range of proteomic technologies are being used in quest for newer approaches which could significantly contribute to the discovery and development of selective and specific cancer biomarkers for monitoring the disease state and anti-cancer therapy success.

Taking into consideration the above aspects, this research was undertaken to study cancer cell proteomes and their changes after anti-cancer treatment with specific focus on: (a) response to conventional anthracycline/anthracenedione drugs with respect to their different clinical efficacy and (b) identification of novel targets for therapy in cancer cells resistant to biological drugs such as inhibitors of (b1) cyclin-dependent kinases and (b2) Aurora kinases.

This study identified several interesting key aspects related to the effects of daunorubicin, doxorubicin and mitoxantrone. With the main focus on early time intervals when the influence of apoptosis is minimised, changes common for all three drugs belonging mainly to metabolic and cellular processes were observed. More importantly, significant changes in proteins involved in the generation of precursor metabolites and energy specific for daunorubicin, transport proteins participating in response to doxorubicin and a group of proteins of immune system characterising response to mitoxantrone were observed. Both a paired comparison and the multivariate evaluation of quantitative data revealed daunorubicin as a distinct member of monitored anthracycline/anthracenedione drugs.

Studies on the development of cancer cell resistance revealed that Rho GDP-dissociation inhibitor 2, Y-box binding protein 1, and the HSP70/90 organizing protein have a critical role to play in resistance to cyclin-dependent kinases inhibitor. The results indicated that various other parameters such as protein truncation and post-translational modification(s) are involved in drug-resistance. Another example focused on resistance to Aurora kinases inhibition underlined the important influence of p53 background functionality of cancer cell resistance and highlighted a direct link of p53-independent mechanism of resistance to CYC116 with autophagy. Importantly, serine hydroxymethyltransferase, serpin B5 and calretinin represent the proteins which may help overcome resistance with a combination therapy approach.

A combination of identified drug specific protein changes, which may help to explain anti-cancer activity, together with the benefit of blocking activation of adaptive cancer pathways, presents important approaches to improving treatment outcomes in cancer. In order to combat cancers, proteomic research derived findings may play a critical role, however, careful interpretation of the results and their relevance to biological and functional parameters need to be carefully considered prior to successful translation into clinic.