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Commentary

PAK6-Associated Support Vector Machine Classifier: A New Way to Evaluate Response and Survival of Gastric Cancer Treated by 5-FU/Oxaliplatin Chemotherapy

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Gastric cancer (GC) is the 4th most common human malignant disease and the second-leading cancer-related deaths in the world (De Manzoni et al., 2016). Treatment with 5-fluorouracil/oxaliplatin (5-FU/oxaliplatin) chemotherapy has proven to significantly improve survival of patients with metastatic GC (Lordick et al., 2014).

In *EBioMedicine*, Jiang et al. in two large cohorts of stage II and III GC patients sought to investigate the correlation among high levels of serine/threonine p21-activated kinase 6 (PAK6) with survival rates and chemosensitivity to 5-FU/oxaliplatin (Jiang et al., 2017). High PAK6 expression correlated with poor prognosis in chemotherapy treated GCs, but it did not show any association in non-chemotherapy treated GCs. Moreover high PAK6 increased chemosensitivity to 5-FU/oxaliplatin.

After the determination of the predictive values of six biomarkers (PAK6, TS, ERCC1, Cox2, Ki-67 and p21^{WAF1}) the authors constructed a support vector machine (SVM) classifier. With the help of this classifier, a subgroup in the stage II and III GC patients was identified that could easily benefit from the 5-FU/oxaliplatin chemotherapy. In fact, the chemotherapy was able to significantly improve disease free survival (DFS) and overall survival (OS) in the high chemotherapy score – CS-SVM classifier; $p = 0.004$, $p = 0.001$ respectively, but it did not in the low CS-SVM ($p = 0.562$, $p = 0.761$) in the validation cohort. Based on the CS-SVM classifier results, a nomogram was developed to create a quantitative method for the clinical prediction of stage II and III GC patients' probability of OS over a 3- and 5-years period of time.

Two merits for the Jiang et al. study should be commended. Although data from literature proved that the highly expressed levels of

PAK6 correlate with poor prognosis in several tumors (Chen et al., 2014; Chen et al., 2015), the authors for the first time confirmed the same role in GC, correlating high levels of PAK6 with a poor OS and a poor DFS. This knowledge could be useful for the development of novel targeted therapies aiming to specifically target PAK6, or its down-stream pathway. Also the exact molecular oncological function of PAK6 in GC deserves further attention in the context of precision medicine development.

The second commendation to the work goes for the development of the CS-SVM method to predict which subgroup of GC responds better to the chemotherapy. This method, if proven useful in multicentre clinical settings, could become a valuable tool to introduce in the clinics to help determining those patients that could respond better to chemotherapy.

Moreover, discovery of additional biomarkers could become crucial in improving this tool to predict GC chemotherapy responders. Determining the relative role of other recognized GC biomarkers could enhance the accuracy of the method. With new and always more advanced technologies, such as the triple quadrupole LC-MS/MS with MRM analysis, the discovery of more biomarkers and the determination of their prognostic values could bring to an always more accurate prognostic tool for chemotherapy responders in GC.

In conclusion, there is the need to improve results of chemotherapy in GC (Petrioli et al., 2015; Roviello et al., 2016), the CS-SVM represents a good method to predict a subgroup of stage II and III GC patients that could better respond to the chemotherapy and determine through a nomogram the probability of patients OS at 3 or 5 years. The discovery of more GC biomarkers in this context could improve the method that if validated in multicentre clinical settings could become a valuable tool to introduce in the clinics, in order to help in the decision-making for taking this type of chemotherapy that could be beneficial in GC patients.

Disclosure

The authors have no potential conflicts of interest to declare.

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