

## **A Proteomic Approach for the Diagnosis of a Pathophysiological Concept of Kampo Medicine**

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We have explored plasma protein biomarkers and/or diagnostic algorithms for “Oketsu”, a pathophysiological concept in Japanese traditional (Kampo) medicine, or a predictive biomarker for the beneficial effect of a Kampo medicine. Rheumatoid arthritis (RA) patients were treated with Keishibukuryogan (KBG), a representative Kampo drug for “Oketsu”. Plasma samples were diagnosed as either having an “Oketsu” or “Non-Oketsu” state as well as American College of Rheumatology (ACR20) response. Protein profiles were obtained by SELDI-TOF MS. Hierarchical clustering and decision tree analyses were performed. KBG treatment for 4 or 12 weeks decreased “Oketsu” scores significantly. SELDI protein profiles gave 266 protein peaks whose expression was significantly different between “Oketsu” and “Non-Oketsu”. Hierarchical clustering gave 3 major clusters (I, II, III). The majority (68.4%) of “Oketsu” samples were clustered into one cluster as the principal component of the cluster I. The remaining “Oketsu” profiles constituted a minor component of the cluster II, all of which were derived from patients cured of the “Oketsu” state at 12 weeks. The decision tree construction addressed the possibility of developing the diagnostic algorithm for “Oketsu”. We used a decision tree that discriminated most correctly responder and non-responder to KBG. The constructed tree, containing two splitters as  $m/z$  9,200 and 15,970, showed accuracy values of 75.6%. These protein markers were identified as Haptoglobin alpha 1 and alpha 2 chains. The present study suggests that the pathophysiological concept of Kampo medicine “Oketsu” has a physical basis in terms of the profile of blood proteins. It may be possible to establish objective criteria for diagnosing “Oketsu” using a combination of proteomic and bioinformatics-based classification methods.