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Variation in global and enhancer-specific DNA methylation profile is an important feature of malignant pleural mesothelioma

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Objectives
Malignant Pleural Mesothelioma (MPM) is a rare cancer of the pleura, primarily attributed to occupational asbestos exposure. Despite the world-wide reduction in asbestos exposure through legislation prohibiting its use, the incidence of asbestos-related cancers such as MPM continues to rise in many countries, in part due to the long latency period between exposure and tumour development. Furthermore, MPM is an extremely aggressive disease with an estimated five-year overall survival rate of 10-12%. In the MESOMICS Project, part of the Rare Cancers Genomics imitative at IARC, we aim to identify molecular characteristics of MPM with a view to better understanding tumour aetiology, and improving clinical classification and management of MPM.

Methods
We generated whole-genome sequencing, RNA sequencing and DNA methylation array data for 124 MPM, covering all three major histological types (epithelioid, sarcomatoid, and biphasic). Using these data we performed an integrative analysis with MOFA (multi-omics factor analysis) to generate a molecular map of MPM, then examined the clinical and molecular characteristics of tumour samples in association with their location on the map.

Results
Integrating gene expression, DNA methylation, copy number, and somatic variant datasets with MOFA resulted in a molecular map of MPM that displayed a continuous profile across the three histological types, rather than distinct clusters. DNA methylation level was found to be the biggest contribution to the first axis of the map, particularly at enhancer elements. DNA methylation data were further analysed by examining the global methylation level, and that of three distinct genomic regions: promoter, enhancer, and gene body. Global methylation level was associated with the more aggressive sarcomatoid histology, an increase in cell proliferation rate, and copy number burden. Methylation level of enhancer regions displayed the most variation across the spectrum of MPM, and was also associated with sarcomatoid histology. Pathway analysis of genes proximal to variable enhancer elements showed enrichment in epithelial-to-mesenchymal transition (EMT), and response to inflammation pathways, and expression of mesenchymal-associated genes was significantly correlated with enhancer methylation level. Lastly, motif enrichment analysis identified differential enhancer methylation in the binding sites of key transcription factors in EMT and inflammatory response pathways.

Conclusion
Through the MESOMICS project we have uncovered a continuous profile of molecular characteristics across the spectrum of MPM. Notably, we have found evidence of global and enhancer-specific DNA methylation profile in driving the development of the most aggressive tumours through promotion of genome instability, and mediating epithelial-to-mesenchymal transition.

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