Factors associated with energy metabolism as potential biomarkers in haematological malignancies

Energy metabolism refers to the processes used by cells to generate and store the energy needed to support their functioning and growth. In cancer cells, an unusual rearrangement of energy metabolism, known as the Warburg effect, is observed. It is characterized by increased reliance of cancer cells on glycolysis, rather than the much more efficient oxidative phosphorylation. Lactate ions are produced as a by-product of glycolysis, and cancer cells need special lactate removal mechanisms to prevent acidosis. Monocarboxylate transporters (MCTs) are proteins responsible for the transport of lactates across the membrane; however, they must interact with basigin to function properly. Basigin (BSG, CD147), a membrane-bound immunoglobulin, is significantly overexpressed in many cancers, and studies show that it supports cancer cell survival mostly by maintaining efficient lactate transport. It is also implicated in other processes associated with cancer, e.g. induction of angiogenesis. BSG is considered a diagnostic and prognostic biomarker in many cancers, and some studies suggest that its soluble form (sBSG) may be an interesting marker on its own. However, little is known about BSG in haematological malignancies. It has been established that it is overexpressed in multiple myeloma (MM) and may have a role in acute myeloid leukaemia (AML).

The aim of this doctoral thesis was to 1) verify if selected genetic variants of BSG and monocarboxylate transporter 1 (MCT1) can affect MM; 2) confirm that BSG and MCT1 are overexpressed in AML and verify if BSG/MCT1 genetic variants, as well as soluble BSG expression, can be potential biomarkers in AML; 3) establish if soluble BSG can be a potential biomarker in MM. Results were described in three corresponding scientific papers.

The first paper describes single nucleotide polymorphisms (SNPs) in the genes coding for BSG and MCT1 in MM patients. Four SNPs were selected in each gene based on an *in silico* analysis. These SNPs were then analysed in a group of 135 MM patients and 135 healthy individuals. BSG alleles rs4919859 C and rs8637 G were significantly associated with better progression-free survival in MM patients, while MCT1 alleles rs1049434 A, rs7556664 A and rs7169 T were associated with better overall survival. Additionally, rs4919859 C, rs8637 G and rs8259 A were more common in patients with more advanced disease at diagnosis. This was the first study that described the BSG rs4919859 SNP and confirmed its predicted effect on disease.

The second paper deals with BSG and MCT1 in AML. Using six model AML cell lines and healthy cells as a control, it confirmed that both genes are overexpressed in most AML models

on the mRNA level. In a study on 37 AML patients and 25 healthy individuals, sBSG was found to be overexpressed in serum of AML patients. Furthermore, high sBSG was associated with worse overall survival, higher blast percentage and higher white blood cell count in AML. Expression of VEGF, a pro-angiogenic factor, correlated with BSG protein expression, potentially confirming the pro-angiogenic role of BSG in AML. Interestingly, sBSG expression correlated neither with BSG mRNA level, nor with total BSG protein production, which can result from the complicated nature of sBSG secretion. Continuing the study on BSG and MCT1 genetic variants in MM, the previously selected SNPs were tested on a group of 92 AML patients and 135 healthy individuals. BSG alleles rs4919859 C and rs4682 C, as well as MCT1 genotype rs1049434 AA were found to correlate with worse overall survival, confirming the adverse effect of allele rs4919859 C.

The third paper describes sBSG expression in MM. For the purpose of the study, samples of 62 MM patients and 25 healthy individuals were used. sBSG level was found to be higher in serum of MM patients and in a subgroup of patients with more advanced disease. Furthermore, its level dropped after positive response to treatment. High sBSG level was associated with worse progression-free survival. mRNA expression was also analysed in a subgroup of MM patients. Similarly to AML, sBSG level did not correlate with BSG mRNA expression in MM patients. However, BSG mRNA expression was confirmed to correlate with MCT1 and VEGF expression.

Results of these studies confirm the involvement of BSG and MCT1 in AML and MM pathogenesis and suggest that their genetic variants, as well as soluble BSG level, may be potential biomarkers in haematological malignancies.