DNA methylation as a prognostic marker in clear cell Renal Cell Carcinoma

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie/medicine doktorsexamen framläggs till offentligt försvaret den 21 februari, kl. 09:00.
Avhandlingen kommer att försvares på engelska.

Fakultetsopponent: Professor/Överläkare, Ralph Peeker, Institutionen för kliniska vetenskaper avd. för Urologi, Sahlgrenska Universitetssjukhuset, Göteborg, Sverige.
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Clear cell renal cell carcinoma (ccRCC) is the most common type of renal cell carcinoma worldwide. Metastatic ccRCC is correlated to poor prognosis whereas non-metastatic disease has a 5-year survival rate up to 90%. Due to increased accessibility to different types of diagnostic imaging the frequency of metastatic ccRCC at diagnosis has decreased since the beginning of the 21st century. This has led to an earlier detection of primary tumors before patients present symptoms. However, 20-30% of the non-metastatic patients at diagnosis will progress and metastasize within five years of primary nephrectomy. Identifying patients at high risk of tumor progression at an early stage after diagnosis is of importance to improve outcome and survival. Currently, in Sweden, the Mayo scoring system is used to divide tumors into low, intermediate or high risk for tumor progression.

DNA methylation has been associated with tumor development and progression in different malignancies. In this thesis, Illumina Infinium HumanMeth27 BeadChip Arrays and Human Meth450K BeadChip Arrays have been used to evaluate the relationship between methylation and clinicopathological variables as well as ccRCC outcome in 45 and 115 patients.

Our studies identified an association between higher level of promoter-associated DNA methylation and clinicopathological variables in ccRCC. There was a significant stepwise increase of average methylation from tumor-free tissue, via non-metastatic tumors to metastatic disease. Cluster analysis divided patients into two distinct groups that differed in average methylation levels, TNM stage, Fuhrman nuclear grade, tumor size, survival and tumor progression. We also presented two prognostic classifiers for non-metastatic tumors; the promoter methylation classifier (PMC) panel and the triple classifier. The PMC panel divided tumors depending on the methylation level, PMC low or PMC high, with significantly worse prognosis in the PMC high group. This data was verified in an independent, publically available cohort. The triple classifier was created using a combination of clinicopathological variables, previously identified CpGs biomarkers and a novel cluster analysis approach (Directed Cluster Analysis). The triple classifier had a higher specificity compared to the clinically used Mayo scoring system and predicted tumor progression with higher accuracy at a fixed sensitivity.

The identification of two epigenetic classifiers that predicted outcome in non-metastatic ccRCC further establishes the role of DNA methylation as a prognostic marker. This knowledge can contribute to identification of patients with a high risk of tumor progression and can be of importance in the decision regarding adjuvant treatment post-nephrectomy.

Keywords
Clear cell Renal cell carcinoma, DNA methylation, Classification, Prognosis, Survival, Genetic aberrations

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