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EDITORIAL

MCM2 and MCM5 as Prognostic Markers in Colon Cancer: A Worthwhile Approach

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In their current report, Theocharis and coworkers analyze the relation of MCM2 and MCM5 with clinicopathology parameters and molecular parameters of cell proliferation and differentiation well established in colon cancer [1]. While they found MCM2 to be consistently associated with clinicopathological parameters, Ki67 and p53, MCM5 was not.

What makes this study so appealing? Besides its concise and straight-forward character, it deals with an interesting molecular parameter, minichromosome maintenance proteins (Mcm). The Mcm family members (Mcm2-7) are highly conserved replication initiation factors. Mcm proteins are presumed to regulate replication by cyclical DNA-unwinding. They are integrated into pre-replicative complexes forming during the G1 phase of the cell cycle. Thereby they "license" chromatin for replication in the subsequent S phase. While Mcm proteins are present in all phases of the proliferative cell cycle, they are absent in quiescent cells and in cellular senescence. The strict relation to chromatin replication renders the Mcm protein family a novel class of proliferation marker [2]. They are currently viewed as highly specific for proliferation [3]. In contrast to Ki67, which was also analyzed in the current contribution by Theocharis, Mcm2 is an essential factor for initiation of DNA replication in eukaryotic cells. Thus Mcm proteins have been suggested as excellent markers for tumor evaluation [4].

However, clinicians may not be overly interested in the definition of novel markers of cell proliferation unless a clinical benefit is involved. As Theocharis and coworkers relate their data on Mcm expression to potential clinical applications their study is appealing to both basic researchers and clinicians.

To date, prognosis of almost all relevant malign diseases is assessed by classical histopathology and clinical parameters. While microscopic staging and histopatholigcal grading reflect tumor biology but only indirectly, only very few molecular parameters directly related to tumor biology have been implemented in the clinical management of cancer. Colorectal cancer remains one of the greatest challenges for medical and surgical oncologists. While colorectal cancer is extraordinarily frequent and responsible for the greatest cancer related mortality in the Western world, the assessment of its prognosis is not satisfactory. Several molecular markers have been evaluated as prognostic factors and were hoped to aid in clinical decision-making, however no molecular marker, genetic signature, or combination of histologic, genetic, and molecular parameters has been established to date [5]. This may be due to the decisive heterogeneity in colorectal neoplasia. Reading the literature on molecular prognostic markers for colorectal cancer as a urologist, I did get the impression that the field is tricky indeed. There are few publications with clear findings to begin with, and colorectal cancer does seem to defy many approaches.

Recently, the same group presently contributing showed that peroxisome proliferator-activated receptor gamma, a key regulator of adipogenic differentiation and glucose homeostasis, participates in the biological mechanisms underlying carcinogenic evolution in the colon. Its expression, however, was not correlated with clinicopathological parameters or outcome [1]. Some molecular parameters depend on the localization within the colorectal tract, which I did not expect. Barrera and coworkers found elevated prolactin levels in colon cancer to be related to an increased risk of mortality, while in rectal cancer, high

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values were significantly associated with survival advantage [6]. Some markers are more promising. Recently, MicroRNA expression was associated with poor survival independent of clinical covariates, including TNM staging, and was associated with a poor therapeutic outcome [7]. However, while the assessment of MicroRNA is rather complex, the methodology underlying Mcm evaluation is a simple immunohistochemical approach. Only feasibly simple methodology will establish markers broadly.

In the management of colorectal cancer, more accurate staging and prognostic tools are demanded to adequately guide therapy [5]. In urology, for example, the prognostic validity current histopathological evaluation of non-muscle invasive bladder cancer is sometimes put in doubt [8]. While histopathology remains the foundation of any evaluation and assessment of prognosis it might be successfully expanded by molecular markers [9, 10]. However, research must continue, since no marker has been widely established in clinical application to date.

This is also true for colorectal cancer, a malign disease with immense significance and complex clinical management. Thus Theocharis and coworkers dwell on a matter of increasing interest to everyone involved in the clinical management of colorectal neoplasm and any malignancy. As the authors state in their present contribution, their findings highlight the need for continuous research and suggest that Mcm expression is promising and may well be a reliable prognostic tool in addition to histopathology in the future.

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