DNA methylation markers for early detection of colorectal cancer

IMPACT PARAGRAPH

SCIENTIFIC IMPACT

Colorectal cancer (cancer of the colon and the rectum, CRC) is the third most frequently diagnosed cancer and the fourth leading cause of oncological death.

Worldwide, there were an estimated 1.8 million incident cases and 896,000 and 881,000 deaths in 2017 and 2018, respectively, resulting in 19.0 million disability-adjusted life-years in 2017 only. The global burden of CRC is expected to increase by 60% by 2030, leading to over 2.2 million incident cases and 1.1 million deaths.

The prognosis of a patient with CRC is highly dependent on the stage of the disease. The 5-year survival rate for early-stage CRC is as high as 90%, dropping to 14% in patients with advanced-stage cancer. Early detection and subsequent management of CRC is an effective strategy to decrease the burden of this disease on the patient and on society.

However, since individuals with early stage CRC are usually asymptomatic, screening (i.e. testing to detect potential health disorders or diseases in people who do not have any symptoms of disease) is an accepted strategy for early detection of CRC.

A variety of invasive and non-invasive CRC screening tests are available such as colonoscopy and fecal blood tests. Colonoscopy is the gold standard, but its invasiveness and associated risks result in poor participation rates. Non-invasive detection of hemoglobin in the stool (fecal immunochemical test (FIT)) is widely used for screening of CRC. Although being implemented as CRC screening test in many countries, the FIT test fails to identify up to 40% of patients and 45-70% of healthy screenees test positive. Molecular markers have been shown to increase the detection rate of CRC patients and are being investigated extensively by the scientific community.

In this thesis we investigated whether we could identify DNA methylation markers that might improve the currently used non-invasive tests. Since we are not the only research group working on this topic and in order to obtain a clear update on the status of the field, we first set out to investigate the studies that have been published in the literature. These updates provided some valuable insights on the translational efficiency of DNA methylation markers for detection of colorectal cancer and cancer in general. The systematic reviews that we performed clearly showed that only a very small percentage (0.8%) of the published caner DNA methylation markers (in general and also specifically for CRC early detection) is actually being used in the clinic. In Chapter 2, 3 and 6, we discussed the causes for this lack of translation, which include the lack of clinical relevance, low quality study design, low quality reporting, low potential to improve the research field and the lack of transfer of academic knowledge to commercial partners. Our observations and conclusions can be used by the

scientific community to design clinically relevant studies that will truly improve the research field, will lead to less scientific waste and will improve the lives of cancer patients. Public calls by other scientists to increase the reproducibility of scientific research [1] and to bridge the translational innovation gap through good biomarker research [2] underscore the importance of our message. In Chapter 4, we used the lessons learned from Chapter 2 and 3 to perform a clinically relevant DNA methylation marker identification study which yielded biomarkers that can improve the currently used tests. Although these markers still need to be validated in large patient series, the markers have been patented and will be developed in collaboration with a commercial partner to translate them into clinically relevant tests.

SOCIETAL IMPACT

Scientific research is funded by governmental organizations, charity organizations and corporations which all aim to spend their money well. It is the responsibility of translational scientists to use the funds that have been entrusted to them wisely and perform research that will benefit the patient and society. This thesis shows that the cancer biomarker scientific community, and more specifically the DNA methylation marker scientists, have to become more effective and waste less resources. Our recommendations in Chapter 2 and 3 can help to better design methylation marker studies that will hopefully enter the clinic faster.

In addition, the biomarkers identified in Chapter 4 (and the improved DNA isolation protocols developed in Chapter 5) might improve the currently used non-invasive tests for early detection of colorectal cancer and identify individuals with colorectal cancers that would not have been detected without the additional DNA methylation markers. Early detection of colorectal cancer and subsequent management of the disease has been shown to save lives and reduce the need for invasive and (neo)adjuvant treatment, thereby improving the quality of life of patients.

REFERENCES

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