Enlightening the importance of the NDRGs in the (cancerous) gut

The gastrointestinal (GI) tract is one of the most complex organs of the human body. With its approximate 5m length, a diversity of specialized epithelial cell types (the 'lining' of the GI tract), about 80% of our immune cells, more than 100 million neurons (the enteric nervous system, ENS) and an extensive array of gut microbiota, the GI-tract forms a barrier between the body's internal and external milieu and ensures successful digestion and absorption of nutrients. It is thus not surprising that (small) deviations in the structure and/or interactions may give rise to "digestive disorders" including (chronic) inflammatory bowel diseases and bowel cancer.

Driven by the knowledge that the N-myc downstream-regulated gene (*NDRG*) 4 is an accurate biomarker for the early detection of colorectal cancer and that it's family members NDRG1 and NDRG2 are involved in the development and maturation of the intestinal tract, we reviewed the importance of the NDRG family (NDRG1-4) in the developing, mature and cancerous gut.

The NDRG proteins share more than 50% similarity and are highly conserved through evolution in a variety of species, yet have a divergent expression pattern in the embryonic and adult gut. NDRG1 is highly present within epithelial cells during intestinal development and maturation. NDRG2, 3 and 4 are, during development, strongly expressed by enteric neuronal crest cells, the precursors giving rise to the ENS, the "brain of the gut". While NDRG4 is still expressed by mature enteric neurons, the adult expression pattern of NDRG3 is currently unknown and the expression of NDRG2 seems to shift towards the epithelium during maturation.

Various studies describing the role of the NDRG family members in colorectal carcinogenesis, elucidate that *NDRG4* and its most similar family member, *NDRG2*, are highly methylated in colorectal cancer. Importantly, this high DNA methylation is responsible for the reduced expression of both genes in the cancerous gut. Similarly, NDRG1 expression, although mainly caused by copy number variations, is also reduced during colorectal cancer. Bringing these data together, these publications highlight the potential significance of *NDRG1*, *2* and *4* as prognostic biomarkers for colorectal cancer (worse overall and disease-free survival) and show that NDRG1 could be a predictive biomarker for the response of colorectal cancer-patients to Irinotecan-based therapy. An important note is that these results fluctuated when using different antibodies, varying experimental techniques and variable population groups, thereby emphasizing the need to validate these outcomes in large-scale studies implementing a standardized study-protocol. In contrast, *NDRG4* DNA methylation currently represents, alone or as part of a the Cologuard®, an established diagnostic biomarker to screen for the early-detection of colorectal cancer.

Functionally, NDRG1, 2 and 4 have different, but mostly tumor suppressive effects during colorectal cancer. Of note, *NDRG1* and *NDRG2*, both expressed in epithelial cells, have been described to affect the key hallmarks of colorectal cancer, for example proliferation, cell death and

the epithelial-mesenchymal transition. Encouraged by the recently proposed hypothesis that the ENS contributes to colorectal cancer as it communicates with several cell types, including tumor cells, we hypothesize that enteric neuronal NDRG4 can affect the intestinal epithelium (and tumor cells) by regulating cell-cell communication.

All together these data show that, except for *NDRG3*, all three *NDRG* family members have the potential to serve as biomarkers for colorectal cancer and have tumor suppressive properties mainly affecting cell growth and the epithelial to mesenchymal transition in the GI-tract. Further studies are needed to elucidate if the NDRGs have similar effects in other tissue or cancer types.

Nathalie Vaes [1], ***Simone L. Schonkeren*** [1], ***Veerle Melotte*** [1,2]
[1]*Department of Pathology, GROW–School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands*
[2]*Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands*

Publication

A combined literature and in silico analysis enlightens the role of the NDRG family in the gut.
Nathalie Vaes, Simone L. Schonkeren, Erwin Brosens, Alexander Koch, Conor J. McCann, Nikhil Thapar, Robert M.W. Hofstra, Manon van Engeland, Veerle Melotte
Biochim Biophys Acta Gen Subj. 2018 Oct