CHAPTER 7

Concluding Remarks

Concluding Remarks

The work-up of patients with an early-onset CRC and/or family history of cancer is an elaborate and time-consuming process that can be intimidating for many primary care providers and specialists. Because of the absence of an overt polyposis phenotype, Lynch syndrome can be the most challenging hereditary colorectal cancer syndrome to recognize, and there are many patients with Lynch syndrome that remain undiagnosed. In **Chapter 3** we show that molecular analysis of colorectal adenomas may have a role in the diagnosis of suspected Lynch syndrome. The combination of both MSI analysis and IHC staining for MMR proteins detected DNA repair deficiency in 73% of the Lynch-associated adenomas, and this included adenomas smaller than 5 mm. Thus, in the workup of patients suspected to have a germline MMR gene mutation, it is reasonable to begin with MSI and IHC analyses of adenomas, and our data suggest that IHC testing alone is nearly as sensitive as a combined approach. Adenoma size does not appear to be consistently correlated with a positive test result, so small adenomas should not be excluded from analysis. Positive results can be utilized to direct germline genetic testing. However, a negative MSI or IHC test result in an adenoma should be interpreted cautiously and cannot be used to formally exclude the diagnosis of Lynch syndrome if other clinical features suggest the diagnosis. Nevertheless, this approach would expand the diagnostic testing options in cases with suspected Lynch and increase the opportunities to recognize the syndrome before the development of invasive cancer.

The clinical behavior of CRCs with MSI is distinctive, and the most intriguing and consistently described feature is the enhanced survival benefit that does not appear to be attributable to differences in therapeutic response. The molecular basis for the prognostic

advantage due to MSI is not clearly established. In **Chapter 6**, we provide a potential molecular explanation for the favorable outcome observed in MSI tumors. We show that *TGFBR2* mutations, observed in up to 90% of CRCs with MSI, interfere with TGF-β-induced EMT, an important component of cancer progression, and therefore reduce the migratory and invasive capabilities of cancer cells. Tumors with MSI but without *TGFBR2* mutations undergo EMT in response to TGF-β1, suggesting that *TGFBR2* genotype and not MSI status *per se* may be the key determinant of the EMT response and ultimately, prognosis. In addition, these findings suggest a rationale for the therapeutic inhibition of TGF-β signaling in MSS colorectal tumors.

Acknowledgements

During my years abroad, I have been fortunate enough to have the help and support of many people and friends without whom this thesis would not have been possible. While most people did not help directly on the project, every one of them contributed in some way towards helping me, and for everyone listed and not listed here I am eternally grateful for their help.

I would like to express my sincere gratitude and appreciation to my advisor Prof. Daniel Chung for his continuous support, patience, motivation, enthusiasm, and immense knowledge. I could not have imagined having a better advisor and mentor.

To my parents, Tommaso and Anna Rita, and my sister Federica. They always stayed behind me, pushed me to be a better person and a better doctor, and most of all suffered my absence.

Last but not the least, to the love of my life, Michele, for his encouragement, understanding, and unconditioned love.

The financial support of the Massachussets General Hospital, ECOR Fund for Medical Discovery, is gratefully acknowledged.