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Immunohistochemical Expression of LRG5 and CD44 in Colorectal Polyps and Adenocarcinomas: Implications for Carcinogenesis

D. Yildiz[1], M. Balci[2], S. Yildiz[3]
[1]*Kırıkkale University Medical Hospital, Department of Pathology, Kırıkkale, Turkey*
[2]*Kırıkkale Medical University, Department of Pathology, Kırıkkale, Turkey*
[3]*Kahramanmaraş Çağlayancerit Public Hospital, Department of Family Medicine, Kahramanmaras/Kırıkkale, Turkey*

Introduction: Colorectal cancer is the fourth ranking cancer worldwide and exhibits two-fold increase in industrialized countries after the age of 40s. Although there are well defined colorectal carcinomas associated with familial syndromes, most of them are sporadic cancers with complex pathogenetic pathways. Although the precise mechanism is still not understood, they arise through a multistep process in which genetic and epigenetic alterations accumulate in a sequential order; so the better defined precursor lesions are adenomatous polyps. The aim of this study is to semiquantitatively detect presence of cancer stem cell related markers LGR5 and CD44 in hyperplastic and adenomatous polyps and also in colorectal carcinomas.

Methods: Paraffin blocks of formalin fixed tissue specimens from 60 archival cases that were comprised of 15 hyperplastic polyps, 15 tubular adenomas, 15 villous adenomas and 15 colonic adenocarcinoma were included in this study. Specific antibodies against LGR5; a G-protein coupled receptor and CD44; a cell-surface glycoprotein were used to assess the stem cell properties via immunohistochemistry. The H-score method assigned a score of 0–300 to each patient, based on the percentage of cells stained at different intensities viewed at various magnifications. All statistical analyses were performed using the SPSS® statistical software. Categorical data are presented as numbers (percent), and comparisons between groups were performed by the One-way ANOVA test was used for comparison of distribution of categorical data between groups. P values < 0.05 were considered statistically significant with a confidence interval of 95%.

Results: The difference in H-score between the hyperplastic polyps, adenomas and adenocarcinomas was statistically significant with either antibody. Villous adenomas showed the highest H-score with LGR-5 immunoreactivity mostly in a diffuse and moderate-to-strong manner with a range of 126–300 (126 ± 252) when compared to hyperplastic polyps ($p = 0.038$), tubular adenoma ($p = 0.008$) and adenocarcinoma ($p = 0.034$). Interestingly, similar H-scores were noted on samples of hyperplastic polyp and adenocarcinoma groups, giving a range of 160-300 (160 ± 257, 173 ± 241, respectively). The weakest frequency for LGR-5 positivity was determined in tubular adenoma cases. CD44 expression was nearly identical between villous and tubular adenomas with moderate to strong staining. H-score for both of these adenomatous lesions were determined as 164 ± 234 for villous, 162 ± 239 for tubular adenomas. Hyperplastic polyps demonstrated reactivity mainly in a weak or focal staining pattern with an H-score 92 ± 183 while adenocarcinomas showed rather weak or moderate immunoreaction ($p = 0.026$).

Conclusion: These data suggest that expression of stem cell markers are not well correlated during adenoma progression. LGR5 and CD44 expressing stem like cells are widely distributed in adenomatous lesions and some hyperplastic polyps. We also noted these markers do not seem to be as closely related to dysplasia or invasive malignancy since lower expressions are identified in carcinomas unexpectedly. However, targeting therapy towards CD44 and LGR5 will bring benefits at adenomatous stage of tumorigenesis when we consider the hierarchically organized adenoma-carcinoma pathway.