Non-Functional P2X7 Receptor: A New Biomarker for Colorectal Cancer

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Abstract

Background: P2X7 is the only extracellular ATP receptor with a broad ligand specificity. It is crucial for the proliferation and survival of tumor cells. However, the role of P2X7 in colorectal cancer (CRC) is still unclear.

Objectives: We examined the expression of P2X7 in CRC tissues and the relationship between P2X7 expression and clinicopathological factors.

Methods: The expression of P2X7 was measured using immunohistochemistry (IHC) in 80 CRC specimens. Clinicopathological factors were evaluated using the chi-square test.

Results: The expression of P2X7 was positive in 47% of the CRC specimens. The positivity rate of P2X7 was significantly higher in tumors of the liver and lung metastases than in those of the primary tumors (P < 0.05). The mean expression score of P2X7 was significantly higher in tumors with lymph node metastases than in those without lymph node metastases (P < 0.05).

Conclusion: The expression of P2X7 was significantly associated with clinicopathological factors in CRC. P2X7 could be a potential biomarker for CRC.

Keywords: P2X7, colorectal cancer, immunohistochemistry, clinicopathological factors.
staining was also seen in some moderately differentiated adenocarcinomas. (Fig. 1D)

Adenomatous polyp
Some adenomatous polyps show strong cytoplasmic stain in dysplastic glands but others showed negative staining. (Fig. 2)

Compared with adenocarcinomas, fewer adenoma subjects showed P2X7 staining (100% versus 82%). All adenomas assessed were mildly or moderately dysplastic, so there was no opportunity to assess severe dysplasia. Furthermore, there was no significant difference between mild and moderate dysplasia with staining (P = 0.156).

Normal colorectal tissue
All of the 20 normal tissue samples were not stained by P2X7 antibody. (Fig. 3)

Discussion
In this study, we have shown a clear separation in non-functional P2X7 receptor staining between colorectal cancer tissues and normal tissues. All of the malignant cells showed positive staining, while all of the normal cells were negative. These results support and add to information on the experience of non-functional P2X7 in cancer and normal specimens from other tissues. As all cancers stained positively, no separation of stage specific differences in staining was possible. We did evaluate cellular location of staining (data not presented), but were again not able to identify any stage specific difference in our data set relating to either nuclear or apical membrane staining. Apparent discrepancies between our colorectal cancer study and studies from other tissues may have several explanations. First, interpretation of nuclear staining requires some experience, and optimal immuno-histochemical preparation. Further experience may identify correlations in patterns of staining on a larger data set such as relating to prognosis or staging. Second, heterogeneity of staining was also evident, making selection of appropriate sections as a basis for comparison with clinical staging somewhat subjective. Finally, colorectal cancer may have intrinsically different biochemistry to other tissues with respect to non-functional P2X7 receptor expression.

Most adenomas were positive for the non-functional P2X7 receptor while others (5/33) were negative. We have only assessed 33 mildly and moderately dysplastic specimens in this study. There was a suggestion that moderate dysplasia was associated with positive staining, underpinning a potentially important biological correlation, which may represent a critical point in the development of neoplasia. These results lend further credence to the suggestion that non-functional P2X7 receptor expression may be a pivotal part of carcinogenesis. Further experience with adenomas will help clarify this. Long-term studies will be needed to establish if patients who have developed P2X7 "positive" adenoma are a cohort more susceptible to cancer, and how this biomarker sits with other molecular changes in the pathogenesis of colorectal cancer.

Another question addressed by the present study was whether the non-functional P2X7 receptor is expressed in the normal cells surrounding a frank cancer. In contrast with prostate cancer, we did not find evidence for a field effect in P2X7 expression from biopsies adjacent to cancer. In the mucosa of the head and neck, as well as the oesophagus, such fields have been detected with dimensions of 7 cm in diameter. In conclusion, in the current study, P2X7 expression had high sensitivity and specificity for colorectal cancer and has shown an intermediate staining pattern in adenomatous polyps. As a result, we need to undertake further studies correlating P2X7 receptor expression with the adenoma-carcinoma sequence and its molecular correlates. Studies of non-neoplastic diseased tissues are also needed.

REFERENCES