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Editorial

Clusterin: a potential biomarker for colorectal cancer

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Clusterin is a heterodimeric, disulfide-linked glycoprotein encoded from a single mRNA that is expressed widely in tissues and is found circulating in the serum.[1,2] Because it has been isolated and cloned from multiple species and studied by a number of laboratories, it has been given multiple synonyms, such as SGP-2, apolipoprotein J, TRPM-2, SP 40-40, gp80 and T64.[3] Clusterin is widely expressed and is relatively abundant in testes, brain, and liver under normal conditions. It has been implicated in several biological processes such as cell-cell interactions, sperm maturation, membrane remodelling, lipid transport, regulation of complement-induced cell lysis, cell damage recovery, apoptosis and tumorigenesis.[2] In a number of tissues, clusterin is expressed during cellular differentiation and development. Clusterin mRNA is induced in the intestinal epithelium at embryonic day 16.5, just after the start of a marked change in the morphology of the epithelium from a stratified endoderm to a columnar intestinal epithelium.[4]

Clusterin gene is absent from the list of 108 genes with elevated expression in colonic tumours, in the serial analysis of gene expression (SAGE) database.[5] Despite this fact, its high expression has been reported in several in vivo cancers, including prostate carcinomas,[6] clear cell carcinomas of the kidney[7] and human breast carcinoma.[8] There is no definitive biochemical evidence to support a specific function for clusterin, except for its role in the modulation of the immune system.[9] Some functions proposed for clusterin may be relevant in the setting of tumorigenesis, such as complement defense, the initiation of apoptosis, and membrane protection. Tumour cells are normally poorly differentiated during uncontrolled proliferation. Lack of differentiation markers in most tumour cells with elevated clusterin expression suggests that clusterin may be one marker for intestinal tumour cells. In various experimental models under different circumstances clusterin may exert antiapoptotic or proapoptotic activities.[2] Some recent observations are consistent with its having an antiapoptotic function. The tumour cells with high apoptotic index are commonly deficient in clusterin expression.[10] In general, clusterin RNA levels are negatively correlated with groups of apoptotic cells in tumours.[8,11,12]

Loss of tumour suppressor APC function initiates tumorigenesis in the intestine.[13,14] There are some results which indicate a strong positive association between elevation of clusterin expression and loss of APC function in tumour cells. The expression of clusterin has been studied at all tumour stages, from microadenomas through invasive adenocarcinomas,[15,16] but not yet in metastatic carcinomas. Very low levels of clusterin antigen were detected in the cytoplasm of normal colonic epithelial cells.

Hyperplastic polyps displayed weak clusterin levels in the crypts. Tubular and villous adenomas showed highly elevated clusterin antigen in the cytoplasm of the apical side in the tumour epithelial cells. In invasive adenocarcinoma the clusterin antigen level was relatively weak compared with that in adenomas. Clusterin antigen could be seen in the intercellular cavities. Unexpectedly, a strong clusterin signal was observed in the cytoplasm of cells of normal human colon crypts adjacent to the adenoma or adenocarcinoma, but not in normal crypts far removed from the tumours or in tumour free colonic tissues. The measurable elevation of antigen production in adenomatous polyps indicates that up-regulation of clusterin occurs very early in human colonic neoplasms.[10] Staining of clusterin protein in the apical cytoplasm of tumour cells and in the intercellular cavities suggests that it may be secreted from the tumour cells. Expression patterns of clusterin at different stages indicate that this protein functions in the maintance and/or progression

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of tumours, but it is not clear whether it plays a role in tumour establishment. Recent data suggest that the controversial data on clusterin function in tumour may be related to the pattern shift of its isoform production.[17] An immunohistochemical observation of surgical colon specimens demonstrated a cell compartment clusterin translocation from the nucleus to the cytoplasm directly related to tumour progression. A nuclear localization found in healthy colonic mucosa is consistent with the involvement of the proapoptotic nuclear form in the regulation of cell cycle progression and in cell death induction. The progression towards high-grade and metastatic carcinoma leads to cytoplasmic clusterin distribution. In high-grade carcinomas with metastatic nodes there is complete loss of the proapoptotic nuclear form and a cytoplasmic overexpression of the highly glucosylated form. However, the precise biological function of clusterin in mechanisms of cell death-survival remains to be defined. Clusterin mediated inhibition of complement-induced cytolysis probably protects carcinoma cells from complement-mediated lysis and contributes to the highly metastatic phenotype of those cells. An experimental study showed that if clusterin is over expressed, it results in the enhanced metastatic potential of renal cell carcinoma.[18]

Furthermore, elevated production of clusterin antigen, if secreted from tumour cells, may be detected in body fluids such as serum. We still cannot say whether clusterin can serve alone for early detection of human colorectal cancer, or must be joined into a set of tumour markers. Further studies are needed to determine the exact function of the different isoforms of clusterin and how changes in their expression may modify properties of tumour cells.

Clusterin's specific expression patterns and correlation with cellular events [cell matrix formation, cell membrane remodelling and cell to cell adhesion] during tumorigenesis can make it a useful diagnostic tool for early detection of human colon cancer. The overexpression of the secreted form of clusterin in highly aggressive tumours or/with metastatic lesions could be a potential prognostic and predictive marker for colon carcinoma aggressiveness.

REFERENCES

1. Rosenberg ME, Silkensen J. Clusterin physiologic and pathophysiologic covciderations. Int J Biochem Cell Biol 1995; 27:633-645.
2. Trougakos IP, Gonos ES. Clusterin/apolipoprotein J in Human aging and cancer. Int J Biochem Cell Biol 2002; 34:1430-1448.
3. Tenniswood MP, Guenette RS, Lakins Y, Mooibroek M, Wong P, Welsh JE. Active cell death in hormone dependent tissue. Cancer Metastasis Rev 1992; 11:197-200.
4. French LE, Chonn A, Ducrest D, Baumann B, Belin D, Wohlwend A, Kiss JZ, Sappino AP, Tschopp J, Schifferli JA. Murine clusterin molecular cloning and mRNA localization of a gene associated with epithelial differentiation processes during embryogenesis. J Cell Biol 1993; 122:1119-1130.
5. Zhang L, Zhou W, Velculescu VE, Kern SE, Hruban RH, Hamilton SR, Vogelstein B, Kinzler KW. Gene expression profiles in normal and cancer cells. Science 1997; 276:1268-1272.
6. Steinberg J, Oyasu R, Lang S, Sintich S, Rademaker A, Lee C, Kozlowski JM, Sensibar JA. Intracellular levels of SGP-2 [Clusterin] correlate with tumour grade in prostate cancer. Clin Cancer Res 1997; 3:1707-1711.
7. Parczyk K, Pilarsky C, Rachel U, Koch-Brandt C. Gp80 [Glusterin, TRPM2] mRNA level is enhanced in human renal clear cell carcinomas. J Cancer Res Clin Oncol 1994; 120:186-188.
8. Redondo M, Villar E, Tores-Munoz J, Tellez T, Morell M, Petito C. Overexpression of clusterin in human breast carcinoma. Am J Pathol 2000; 157:393-399.
9. Jenne DE, Tschopp J. Clusterin: the intriguing guises of a widely expressed glycoprotein. Trends Biochem Sci 1992; 17:154-159.
10. Chen X, Halberg R, Ehrhardt W, Torrealba J, Dove W. Clusterin as a biomarker in murine and human intestinal neoplasia. PNAS 2003; 100:9530-9535.
11. Frence LE, Wohlwend A, Sapino AP, Tschopp J, Schifferli JA. Human gene clusterin expression is confined to surviving cells during in vivo programmed cell death. J Clin Inv 1994; 93:877-884.
12. Sensibar JA, Sutkowski DM, Rafflo A, Butyan R, Griswold MD, Sylvester SR, Kozlowski JM, Lee C. Prevention of cell – death induced by tumour necrosis factor alpha in LNCaP cells by overexpression of sulphated glycoprotein -2 [clusterin]. Cancer Res 1995; 55:2431-2437.
13. Liefers GI, Tollenaar RA. Cancer genetics and their application to individualised medicine. Eur J Cancer 2002; 38:872-879.
14. Yang VW. APC as a check point gene: the beginning or the end? Gastroenterology 2002; 123:935-939.
15. Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. Cell 1996; 87:159-170.
16. Halberg RB, Katzung DS, Hoff PD, Moser AR, Cole CE, Donehower LA, Jacoby RF, Dove WF. Tumorigenesis in the multiple intestinal neoplasia mouse: redundancy of negative regulators and specificity of modifiers. Proc Natl Acad Sci USA, 2000; 97:3461-3466.
17. Pucci S, Bonanno E, Picchiorri F, Angeloni C, Spagnoli LG. Modulation of different clusterin isoforms in human colon tumorigenesis. Oncogene 2004; 23:2298-22304.
18. Miyake H, Gleave ME, Arakawa S, Kamidono S, Hara I. Introducing the clusterin gene into human renal cell carcinoma cells enhances their metastatic potential. J Urol 2002; 167:2203-2208.