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Symposium 1

Relevant topics in molecular pathology

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Cancer as a molecular disease of mucins and mucin glycosylation

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Mucins are major glycoproteins of the mucous gels that protect mucosae from environment and are essentially composed by a core protein backbone and 0-linked oligosaccharide attached to serine or threonine. The assembly of a mature mucin implies the coordinated participation of many gene products. Activation of genes coding for the apomucin and for individual glycosyltransferases, with unique donor-substrate specificity, are responsible for the large diversity of the final end product. Interindividual diversity of mucins is determined by the polymorphic nature of mucin genes and by the ABO histoblood group and secretor genes. Further intraindividual, tissue-specific diversity is dependent upon the activation of different mucin and glycosyltransferase genes. Furthermore, consistent alterations of the pattern of mucin expression are observed in cancer tissues.

Our group has been involved in the study of mucins and glycosyltransferases using the following different approaches: i) massive sequencing of complementary DNA libraries from gastric tissues and analysis of ESTs databases to identify new genes involved in the glycosylation pathway. We have so far identified, cloned and demonstrated the enzymatic activity of novel genes of a family of human 34-galactosyltransferases and of a family of 33-galactosyltransferases (1, 2); ii) characterization of mucin genes polymorphism (MUCi and MUC6) in healthy populations and in patients with gastric cancer. Our data show that individuals with a small number of tandem repeats, with smaller glycoprotein products, have an increased riskfor gastric carcinoma development (3, 4); ii) production and characterization of monoclonal antibodies to human mucins using synthetic peptides and *in vitro* GalNAc-glycosylated glycopetides. We have characterized a panel of antibodies to MUCi and produced antibodies to MUC2, MUC5AC and MUC6. Our results show that there are marked alterations in the mucin expression profile observed in intestinal metaplasia. gastric polyps and gastric carcinomas, including the aberrant expression of underglycosylated forms of the MUCi mucin in carcinomas (5-10); and iv) characterization of carbohydrate changes during gastric carcinogenesis.

We found that i) the expression of simple mucin-type carbohydrates is a cancer-associated phenomenon and frequently a marker of cancer progression (11-16); ii) the expression of dimeric sialyl-Lex correlates with venous invasion and poor outcome of gastric cancer patients (17); and ii) we still do not know the meaning of the aberrant expression of histoblood group A antigens and A enzyme in gastric carcinomas of blood group 0 individuals (18).

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Molecular mechanisms in diffuse-type gastric carcinoma: Diagnostic and therapeutic aspects

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Changes in the expression and function of adhesion molecules are important characteristics in the development of gastrointestinal malignancies and might be used in the future as prognostic factors or as new targets in diagnosis and therapy. E-cadherin is a homophilic cell adhesion molecule linking polarized epithelial cells and maintaining the structural integrity of an epithelial monolayer (1). Frequent somatic E-cadherin gene mutations in diffuse type gastric cancer and tumors with markedly diminished or complete loss of homophilic cell-to-cell interactions have previously been demonstrated (2). Partial or complete in-frame deletions of exons expected to be critical for E-cadherin function were detected as well as several point mutations. In about 20% of the cases in-frame deletion of exon 8 or 9 was observed. Very recently, several groups reported germilne E-cadherin mutations predisposing to early onset diffuse-type gastric carcinoma (3-5).

As somatic E-cadherin mutations have been detected in primary tumors and lymph node metastases of gastric cancer patients but were not seen in nontumorous tissues from these patients they