Review Article

Cyclin D1 and Its Expression in Neoplastic Gall Bladder Lesions

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ABSTRACT

Carcinoma of Gall bladder is an infrequent tumour of the gastrointestinal tract and has long been recognized as a highly lethal disease. Tumour markers are glycoprotein that can be determined in blood, saliva, urine and tissues by certain immunological methods. Cyclin D1 is such a marker which is seen to be expressed in various neoplasms. Its role has also been confirmed in gall bladder neoplastic conditions. The onset and progression of gallbladder carcinoma are accompanied with multiple genetic changes that result in qualitative and quantitative alterations in individual gene expression. Immuno-histochemical methods can be used to analyze cyclin D1 levels in gallbladder carcinomas, adenomas and cholecystitis to evaluate their relationships with the pathogenesis, development and metastasis of gallbladder carcinoma.[9]

Keywords: Cyclin D1, Neoplastic, Gall bladder lesions, Tumour markers.

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BACKGROUND AND REVIEW

With the increase in cases of neoplasm, both primary and recurrent worldwide there lies importance of aid which will provide both sensitive and specific diagnosis and prognosis of the condition. Also, it must provide monitoring of on-going treatment. With the detection of tumor marker all these criteria can be easily fulfilled. Tumor markers are glycoprotein that can be determined in blood, saliva, urine and tissues by certain immunological methods. Cyclin D1 is such a marker which is seen to be expressed in various neoplasms. Its role has also been confirmed in gall bladder neoplastic conditions. Certain studies have confirmed their role in progression of tumour and also in poor prognosis. In this article we have

gathered data from literature about cyclin D1 and its role in carcinogenesis.

Carcinoma of Gall bladder is an infrequent tumour of the gastrointestinal tract and has long been recognized as a highly lethal disease.[1-2] It was first described by Stoll in 1777. More than 200 years later, late diagnosis and absence of effective treatment for many patients remain typical features of this disease. The clinical course of patients with gallbladder cancer has been characterized by an initial period of silent progression and a subsequent rapid deterioration. The prognosis is poor—only about a 32 percent five-year survival rate for lesions confined to the gallbladder mucosa and a 10 percent one-year survival rate for more advanced stages.[1-3]

A tumour marker is a substance, the concentration of which can be related to the presence or progress of a tumour. It does not necessarily have to be tumour-specific but may be a substance secreted (into blood or serous fluids) or expressed (at the cell surface) in larger quantities by malignant cells or their environs than by their normal counterparts and may thus represent a relative rather than an absolute marker of malignancy. Tumour markers are usually glycoproteins which are detected by monoclonal antibodies. Each tumour marker has a variable profile of usefulness for screening, determining, diagnosis and prognosis, assessing response to therapy, and monitoring for cancer recurrence.[4-5]

Multiple genetic or epigenetic changes contribute to the multistep process of human carcinogenesis, and some of these changes help with the monitoring of this multistep process. It is important to understand the carcinogenic process and its corresponding molecular basis for each type of cancer. In mammalian cells, the cell cycle controls the progression of replicating cells by the sequential formation, activation, and subsequent inactivation of a series of specific cyclin dependent kinase (CDK) complexes. Cell cycle regulators more often altered in cancers are those controlling G1-S-phase progression. G1-S transition is controlled through interaction of several types of molecules, including CDKs, their positive regulators, cyclins (cyclins D1, D2, D3, and E), and their negative regulators, CDK inhibitors and retinoblastoma protein. CDK inhibitors fall into two classes on the basis of their sequence homology. Among these proteins controlling the G1-S transition, cyclin D1 is one of the most strongly implicated in tumorigenesis. Cyclin D1 exerts its effects on cell cycle progression via two mechanisms:
(a) cyclin D1-CDK complexes inactivate retinoblastoma protein by phosphorylation; and
(b) these complexes bind and sequester Cip/Kip proteins stoichiometrically.

Evidence for the oncogenic potential of cyclin D1 is provided by studies with numerous models, in which elevated expression of cyclin D1 shortens the G1 phase of the cell cycle and enhances malignant transformation. There are three types of D cyclin (Dl, D2, and D3), and they are in part cell type specific, with most cells expressing D3 and either Dl or D2. The most frequent abnormalities relate to cyclin D1. Cyclin Dl is encoded by the CCNDl gene on chromosome llql3, which, has been identified as the PRADl proto-oncogene and as the most likely candidate for the BCL7 proto-oncogene. The connections between the D-type cyclins and tumorigenesis are strengthened by compelling evidence that D-type cyclins are fundamental to cell cycle regulation of the tumour suppressor protein.[5-8]

The disturbances in specific cyclins, CDKs, or the inhibitory proteins play an important role in several types of human cancer. Cyclin D1 over expression, either with or without gene amplification, has been shown in a variety of human malignancies, including breast, colon, lung, oesophageal, liver, pancreatic, tongue, oral verrucous, pharyngeal, and laryngeal cancers and has been identified as a prognostic biomarker for breast, lung, oesophageal, pancreatic, tongue, pharyngeal, and laryngeal cancers. For gallbladder carcinogenesis, the dysplasia to carcinoma and adenoma to carcinoma conventional progressions have been generally ascertained.[5, 9]

The onset and progression of gallbladder carcinoma are accompanied with multiple genetic changes that result in qualitative and quantitative alterations in individual gene expression. Immuno-histochemical methods can be used to analyse cyclin D1 levels in gallbladder carcinomas, adenomas and cholecystitis to evaluate their relationships with the pathogenesis, development and metastasis of gallbladder carcinoma.[9]

Various studies have been recorded in literature which has marked the association of Cyclin D1 in gallbladder neoplasm:

- In a cross-sectional study by Arevalo et al.[10] authors found D1 cyclin is apparently a common pathway involved in the genesis of adenomas and adenocarcinomas of the gallbladder where the expression of marker occurred in 83.3% of adenocarcinomas and in 16.6% of adenomas.
- Feng et al.[11] in their study concluded that expressions of Cyclin D1 increased along with progression of gallbladder mucosa hyperplasia; and showed highest expression in cancer group. Hence, the change of these signals have effect on breaking the balance of proliferation and death of gallbladder epithelial cells, even on inducing gallbladder cancer.
- Hong-Bing Ma et al.[9] suggested in their research that Cyclin D1 may play a role in the early stage of gallbladder carcinoma where they found the expression rates of abnormal cyclin D1 in gallbladder carcinoma (68.3%) and gallbladder adenoma (57.1%).
- Gang Ren et al.[12] found 48.3% expression of Cyclin D1 in cancerous tissue of Gall bladder which is suggestive as an unfavourable prognostic marker.
- AM Hui et al.[8] concluded that Cyclin D1 overexpression is an early event in gallbladder carcinogenesis and independently predicts decreased survival for patients with GBC.
- YH Xuan et al.[13] found aberrant expression of cyclin D1 in adenomas, also, expression of cyclin D1 was elevated in low-grade dysplasias.
- Itio et al.[14] concluded that nuclear cyclin D1 overexpression is a critical event importantly associated with cell proliferation and invasive growth in gallbladder carcinogenesis, and that cyclin D1 immunostaining may become a useful marker for evaluating gallbladder carcinomas.

Therefore, considering the above-mentioned studies it is well understood that Cyclin D1 expression is conclusive of gall bladder neoplasm and its role in pathogenesis. Disruption of the cyclin D1/p16INK4-pRb pathway plays an important role in the progression of gallbladder carcinoma. Serum markers aids in early detection of primary as well as recurrent neoplasm thus they play an important diagnostic as well as prognostic tool.

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