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Novel Angiotens in Receptor Blocker, Azilsartan Induces Oxidative Stress and NFkB-Mediated Apoptosis in Hepatocellular Carcinoma cell line HEPG2

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Introduction

Overexpression of Renin-Angiotensin System (RAS) and Nuclear Factor-Kappa B (NF-kB) has a key role in various cancers. Blockade of RAS and NF-kB pathway has been suggested to reduce cancer cell proliferation. This study aimed to investigate the role of angiotensin II and NF-kB pathway in liver Hepatocellular Carcinoma Cell Line (HepG2) proliferation by using azilsartan (as a novel Ag II antagonist) and Bay11-7082 (as NF-kB inhibitor). HepG2 cells were treated with different concentrations of azilsartan and Bay11- 7082. Cytotoxicity was determined after 24, 48, and 72 h by MTT assay. Reactive Oxygen Spices (ROS) generation and cytochrome c release were measured following azilsartan and Bay11-7082 treatment. Apoptosis was analyzed qualitatively by DAPI staining and quantitatively through flow cytometry methodologies and Bax and Bcl-2 mRNA and protein levels were assessed by real-time PCR and ELISA methods, respectively. The cytotoxic effects of different concentration of azilsartan and Bay11-7082 on HepG2 cells were observed as a reduction in cell viability, ROS formation, cytochrome c release, and apoptosis induction. These effects were found to correlate with a shift in Bax level and a downward trend in the expression of Bcl-2. These findings suggest that azilsartan and Bay 11- 7082 in combination or alone have strong potential for development as an agent for prevention against liver cancer after further studies. Hepatocellular carcinoma is the most common type of primary liver cancer in adults and is currently the most common cause of death in people with cirrhosis. HCC is the third leading cause of cancer-related deaths worldwide It occurs in the setting of chronic liver inflammation, and is most closely linked to chronic viral hepatitis infection (hepatitis B or C) or exposure to toxins such as alcohol, aflatoxin, or pyrrolizidine alkaloids. Certain diseases, such as hemochromatosis and alpha 1-antitrypsin deficiency, markedly increase the risk of developing HCC. Metabolic syndrome and NASH are also increasingly recognized as risk factors for HCC. As with any cancer, the treatment and prognosis of HCC vary depending on the specifics of tumor histology, size, how far the cancer has spread, and overall health. The vast majority of HCC and lowest survival rate after treatment occurs in Asia and sub-Saharan Africa, in countries where hepatitis B infection is endemic and many are infected from birth. The incidence of HCC in the United States and other developing countries is increasing due to an increase in hepatitis C virus infections. It is more than four times as common in males as in females, for unknown reasons. Most cases of HCC occur in people who already have signs and symptoms of chronic liver disease. They may present either with worsening of symptoms or may be without symptoms at the time of cancer detection. HCC may present with non-specific symptoms such as abdominal pain, nausea, vomiting, or feeling tired. Some symptoms that are more associated with liver disease include yellow skin (also called jaundice), abdominal swelling due to fluid in the abdominal cavity, easy bruising from blood clotting abnormalities, loss of appetite, unintentional weight loss, abdominal pain, nausea, vomiting, or feeling tired.

Diabetes mellitus

The risk of hepatocellular carcinoma in type 2 diabetics is greater times the nondiabetic risk) depending on the duration of diabetes and treatment protocol. A suspected contributor to this increased risk is circulating insulin concentration such that diabetics with poor insulin control or on treatments that elevate their insulin output (both states that contribute to a higher circulating insulin concentration) show far greater risk of hepatocellular carcinoma than diabetics on treatments that reduce circulating insulin concentration. On this note, some diabetics who engage in tight insulin control (by keeping it from being elevated) show risk levels low enough to be indistinguishable from the general population. This phenomenon is thus not isolated to diabetes mellitus type 2, since poor insulin regulation is also found in other conditions such as metabolic syndrome (specifically, when evidence of nonalcoholic fatty liver disease or NAFLD is present) and again evidence of greater risk exists here, too. While there are claims that anabolic steroid abusers are at greater risk (theorized to be due to insulin and IGF exacerbation, the only evidence that has been confirmed is that anabolic steroid users are more likely to have the

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benign hepatocellular adenomas transform into the more dangerous hepatocellular carcinoma.

Pathogenesis

Hepatocellular carcinoma, like any other cancer, develops when epigenetic alterations and mutations affecting the cellular machinery cause the cell to replicate at a higher rate and/or result in the cell avoiding apoptosis In particular, chronic infections of hepatitis B and/or C can aid the development of hepatocellular carcinoma by repeatedly causing the body's own immune system to attack the liver cells, some of which are infected by the virus, others merely bystanders. Activated immune-system inflammatory cells release free radicals, such as reactive oxygen species and nitric oxide reactive species, which in turn can cause DNA damage and lead to carcinogenic gene mutations. Reactive oxygen species also cause epigenetic alterations at the sites of DNA repair.

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