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DESCRIPTION (provided by applicant): Hepatocellular carcinoma (HCC) is the third leading cause of cancer death worldwide. Liver cancer in Hispanics and Blacks is 2 to 4 times more frequent than in Whites. Obesity increases the risk of liver cancer by 4.5 folds and is expected to become a leading cause of liver cancer in the US in the future. We recently showed that lipopolysaccharide (LPS) from gut bacteria and its receptor, Toll-Like Receptor 4 (TLR4), promote liver cancer driven by chronic injury. Furthermore, TLR4 ligands LPS and HMGB1 increase in obesity, and fatty livers have higher responsiveness towards LPS. Altogether, these results suggest that TLR4 may contribute to obesity-driven hepatocarcinogenesis. The objectives of this proposal are (1) to study the mechanisms by which obesity promotes liver cancer with a particular focus on the TLR4 pathway, and (2) to further the training of the minority applicant to allow him to become an independent investigator in cancer research. The immediate career goal of the principal investigator (PI) is to acquire the skills, credentials, and preliminary results necessary to successfully obtain independent funding. His long-term goal is to make relevant contributions to the understanding, prevention, and treatment of cancer. The PI has trained as a physician and has conducted basic research in obesity and liver diseases. He plans to bring together these two areas of expertise to investigate how obesity promotes liver cancer. This is a new area of investigation, which will provide him the basis for a future independent research program. The PI will gain the needed skills in three different ways: (1) Through training from his mentors, Drs. Schwabe and Wang, two well-established researchers in GI and liver diseases and cancer, and an advisory committee that includes leading cancer, obesity and Toll-like signaling experts. (2) Through formal coursework to enhance his scientific training, grant writing skills, and skills for an independent career. (3) Through presentation of hs results at external scientific meetings, networking in the Tumor Microenvironment scientific community, and publication in high impact journals. The PI will train at Columbia University, a world leading institution in biomedical research, which has a well-developed program to support its scientists and promote their career development. This scientific proposal will investigate how obesity promotes liver cancer, a question that falls within one of NCI's Provocative Questions: "How does obesity contribute to cancer risk?" The proposal will characterize the contribution of TLR4 to obesity-driven HCC in three separate Aims, which investigate: the contribution of TLR4 to obesity-driven HCC (Aim 1), the TLR4-expressing cell type that promotes HCC (Aim 2), and the TLR4 ligand that promotes HCC (Aim 3). The proposal employs cutting edge technology such as novel Cre-transgenic mice for deletion in specific hepatic cell populations, and novel transgenic mice for conditional ablation of TLR4. Results from the proposed studies will provide a better understanding of how obesity promotes liver cancer and may point to targets for treatment.