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Human Ecdysoneless: A Novel Cellular Mediator of Oncogenesis

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Cancer is a highly complex disease that results from mis-regulation of the interplay between several intracellular and extracellular factors. Although, over the years, several hundreds of these factors are identified and studied, many factors are still unknown. One of the major focuses of our work is to delineate the molecular mechanisms of early steps in transformation of mammary epithelial cells with the goal to identify novel molecular diagnostic/prognostic markers and potential therapy targets of breast cancer. We have reported earlier that HPV16 E6 is highly efficient for hMEC immortalization. Subsequently, we have identified several novel factors including human Ecdysoneless (Ecd), as HPV E6 interacting proteins that might mediate hMEC immortalization. Here, we present results from functional studies of Ecd using in vitro (cell culture) and in vivo (knockout mouse) approaches. We generated a conditional Ecd knockout mouse model and observed that complete deletion of Ecd leads to early embryonic lethality in mice. The experiments using conditional Ecd-null MEFs created from $Ecd^{lox/lox}$ mice revealed that lack of Ecd inhibits cellular proliferation by delaying G1-S cell cycle progression and down-regulating expression of E2F target genes. Furthermore, Ecd directly binds to Rb at the pocket domain and disrupts the interaction of Rb with E2F, leading to an impairment of the repressive effect of Rb on E2F target promoters. Thus, we demonstrate that Ecd is an essential protein in embryonic development and a novel regulator of G1-S cell cycle transition by modulating Rb/E2F pathway. Consistent with these observations, overexpression of Ecd in hMECs hastens the exit of cells from G1 phase of the cell cycle. We have now generated transgenic mouse model that conditionally over express Ecd in mammary tissue to study its role in disease onset and progression. We have generated a highly specific monoclonal antibody against Ecd and have recently used it to analyze Ecd expression in breast cancer specimens. The analyses showed that Ecd is overexessed in ductal carcinoma in situ as well as in infiltrating ductal carcinoma of breast. These observations further demonstrate the link between Ecd expression and cancer. In conclusion, Ecd plays an important role in cell cycle progression and its deregulation can lead to abnormal cell proliferation contributing to breast cancer progression.

Biography

Channabasavaiah B Gurumurthy's education includes a Doctor of veterinary medicine, Master of veterinary medicine and a PhD in veterinary virology from Indian Veterinary research Institute. He obtained his masters and post graduate degrees with distinction and was a gold medalist during his Masters program. Dr. Gurumurthy also received the best student award in addition to securing junior and senior research fellowships from Government of India. His post-doctoral training at Northwestern University, Illinois USA was in Cancer Biology and as a result of over 16 years of research experience, Dr. Gurumurthy got an excellent opportunity to learn and practice advanced biotechnology and molecular biology techniques including designing and generation of transgenic and knockout mouse models. His expertise in advanced genetic engineering has helped him constantly adapt novel, cutting-edge techniques that can be applied to mouse genome engineering to create disease specific mouse models. Particularly his work during post doctoral research at Northwestern University Illinois (2004-2007), and the Faculty Instructor position at the University of Nebraska Medical Center, Omaha, NE (2007-2010), has resulted in development of 6 mouse models for cancer research. In the year 2010, because of his outstanding contributions in the development of transgenic and knock-out mouse models, he was recruited as the Director of the mouse genome engineering core facility at the University of Nebraska Medical Center and Assistant Professor in the department of Genetics Cell Biology and Anatomy, Omaha, NE. During his research career he has received many awards such as post doctoral training award from Department of Defense, The Illinois Mathematics and Science Academy (IMSA) Mentoring Award for mentoring undergraduate students in the Art and Science. Most recently, Dr. Gurumurthy received University-Industry R&D Partnership grant award from Nebraska EPSCoR (Experimental Program to Stimulate Competitive Research), a National Science Foundation support for the state of Nebraska, to generate novel and versatile mouse models for use in basic and biomedical research.