



Recent Discoveries in Orphan Drugs

Nicola Funel

University of Milan, Italy

Abstract:

The present study investigated eight rice lines (Rupsal, Nagalmutha, Polai, Ravana, Marishal, Talmugra, Kamini and Raspanjar) collected from coastal region of eastern India for salinity tolerance through phenotypic and genotypic screening. Among these, three rice lines as highly tolerant (Talmugra, Marishal and Kamini), three tolerant (Rupsal, Polai and Raspanjar) and two moderately tolerant (Ravana and Nagalmutha) to salt stress were identified in phenotypic screening. Pokkali was categorized as tolerant under salinity condition (12 EC dS m⁻¹). In PCR screening using microsatellite (SSR) markers located within Saltol locus, we documented new allelic pattern in selected highly tolerant and tolerant genotypes with RM8094 marker as compared to Pokkali. Besides, another marker RM10694 was found to associate with selection of salinity tolerant genotypes similar to Pokkali. In gene expression studies, no significant difference linked with abscisic acid (ABA), calcium dependent proteins kinase (CDPK), ionic and osmotic signaling pathways in salinity tolerant genotypes was found as compared to sensitive line (IR29). Induction of AP37 gene expression differentiated Kamini and Marishal genotypes from other tolerant and sensitive lines. Peripheral myelin protein 22 gene (PMP22) encodes a membrane protein of myelin in the peripheral nervous system, and PMP22 duplication causes the Charcot-Marie-Tooth 1A (CMT1A) phenotype. PMP22 is also capable of delaying the transition from G0/G1 to S phase (Growth Arrest Specific Gene 3, GAS3). However, growth factors involved in PMP22 regulation, such as Insulin-like growth factor-II (IGF-II), are up-regulated after radiation in fibroblast cells, and might influence chemo-radiosensitivity. Since the compound NSC-631570 had a protective effect on human fibroblasts but not human tumour cells against ionizing radiation, and showed beneficial effects in phase II studies in metastatic and locally advanced PDAC patients. Objective: the aim of this study was to evaluate the interaction between PMP22, IGF-II and NSC-631570 in PDAC Primary Cell Cultures (PCCs). Methods: DNA



duplication of PMP22 gene was evaluated by PCR and specific digestion by the endonucleases EcoRI and NsiI in 13 PDAC tissues, 2 PCCs and PBMCs from 3 healthy subjects (used as negative controls in genetic tests for the CMT1A syndrome). PMP22 protein expression was evaluated in tissues and cells by ImmunoHistoChemistry (IHC), using a quantitative scoring (eg, 0 absent, 1 low, 2 intermediate and 3 high expression). The PCCs were also exposed to IGF-II, NSC-631570, and their combination. Finally, expression of PMP22 was correlated with cell proliferation index. Results. The PMP22 duplication was observed in 44% (7/16) of PDAC patients and in both PCCs. PDAC duplicated samples showed significantly higher score of PMP22 protein expression (p=0.0262). PMP22 protein was correlated with decreased cell growth, whereas 400 nM IGF-II reduced PMP22 expression and increased cell proliferation. Conversely, the addition of 1 μM NSC-631570 increased PMP22 expression, and overcame IGF-II induced proliferation. Conclusion. This is the first study reporting PMP22 duplication in PDAC specimens and cells. This duplication was correlated with PMP22 expression. PMP22 protein was inversely related to cell proliferation and its inhibition by IGF-II might explain chemo-radioresistance caused by PDAC associated fibroblasts. However, NSC-631570 increased PMP22 expression and might synergize with anticancer treatments against PDAC.

Biography:

Nicola Funel received his graduation in Bio-Molecular Science (2000) from Pisa University, Italy, where he acquired his PhD in Experimental and Molecular Oncology (2006) and Specialization in "Clinical Pathology" (2008). Since 2007 he has been working in Surgical Pathology division (University of Pisa), where he involved in Pancreatic Ductal Adeno Carcinoma (PDAC) projects. In 2011 He is council member of Italian Society for Pancreas Study (AISP). He awarded six times from AISP at the annual meeting as "young investigator". He received a grant as "Young Investigator 2013" from "Fondazione Veronesi" Milan, Italy (H-index: 27).

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