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**CANCER STEM CELLS DEDIFFERENTIATION AS THE CORNERSTONE OF TUMOR RELAPSE AND DISEASE PROGRESSION**

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Cancer stem cells (CSCs) are the orchestrators of the intricate communication pathways hijacked by tumors to overcome the inefficiency of the invasion-metastasis cascade. Their plasticity and boosted defense mechanisms permits their survival to the current therapeutic regimens, thus retaining the potential to drive tumor relapse. After observing that the malignant human bronchial epithelial RenG2 cells dedifferentiated following culture in the subcutaneous mouse lumbar region, co-cultures of mice lumbar fibroblasts with RenG2 cells were established and the conditioned media was studied. Results showed Interleukin-6 (IL-6), Granulocyte colony-stimulating factor (G-CSF) and Activin-A were the mediators of the aforementioned intercellular communication process, which prompted the study of the individual role of each cytokine and of exosomes in the overall process. To this end the same co-cultures were reproduced in the presence of combinations of specific cytokine-communication blockers and exosome-mediated communication inhibitors. Whenever exosome's release was blocked, dedifferentiation was abrogated. Additionally, only IL-6 and Activin-A were endowed with the potential to orchestrate dedifferentiation, as when at least one of these cytokines was present a stem cell population developed inside RenG2 cells. G-CSF only maintained CSC's undifferentiated phenotype, as a larger pool of CSCs was attained whenever this cytokine and either IL-6 or Activin-A was present. The attained results implicated IL-6 and Activin-A in the formation of CSCs by dedifferentiation and G-CSF as a potent keeper of the dedifferentiation status. The scavenging of these cytokines from the tumor microenvironment presents a new avenue for therapeutic intervention aiming CSCs ablation and metastasis abrogation.

## BIOGRAPHY

Carlos FD Rodrigues has been graduated from the University of Coimbra, Portugal as both Medical Doctor and a Biologist. He holds a PhD in Biomedicine and Experimental Biology and a Master in Medicine from the same university. Currently he is taking his specialization in Internal Medicine in the Centro Hospitalar do Baixo Vouga, Portugal while continuing his research both at his Hospital in Aveiro and at the Center for Neuroscience and Cellular Biology in Coimbra, Portugal.

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