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Título:

Evaluating novel mechanisms for intercellular communication: from cytoneme formation to signal function.

Resumen de la Memoria:

How cells communicate and achieve organization in a multicellular context is a major question for cell and developmental biologists. In animals, regulation of differential signalling among just six molecules (FGF, EGF, Hedgehog, Wnt, Delta and TGF-B) coordinates a wide range of developmental processes. During my research career I have developed a special interest in the mechanisms for inter-cellular communication and their impact during development, achieving great signal variation with just a few signalling molecules. My own work has established the role of a novel mechanism for signalling at a distance, involving cellular protrusions called cytonemes that spatially restrict the morphogen Hedgehog (Hh) signal, challenging long established free diffusion models. In addition, I have identified exosomes as the vehicle for the Hh molecule's distribution via cytonemes, further revealing a regulated mechanism for release and transport. My recent pilot research focuses on the intracellular regulation of cytoneme formation, and importantly has found a link with a second signalling pathway, the Epidermal Growth Factor (EGF) which implicates pathway cooperation or crosstalk and further increases variation in signal function.

I propose research on the formation and regulation of specialized cytoplasmic projections called cytonemes as an emerging mechanism both for signalling at a distance and for signal crosstalk in a tissue. Importantly, cytonemes are higly dynamic and plastic structures, hence the study of their regulation is fundamental to understand signalling undercurrents. I intend to determine the molecular mechanisms and interactions involved in Hh cytoneme establishment, leading to fundamental knowledge of how signalling is controlled in a tissue during development and potentially in disease.

In cancer, cooperation of the EGF Receptor (EGFR) and Hedgehog (Hh) pathways promotes cell transformation and cell proliferation. Yet, despite its importance, this cooperative mechanism has been poorly explored under normal development. There is evidence of Hh paracrine signalling in tumour development, but cooperation between the two signals in mammalian cancer models has only been described at transduction level within individual cells. I will explore a new perspective on cooperation through cytoneme regulation, where activity of one pathway (EGF) affects the signal outcome of a second (Hh) over neighbouring cells, in the multicellular systems of tissues and tumours during development (Drosophila model) and disease (mammalian cancer model).

I will achieve this by combining genetics, cell biology and proteomics to study cytoneme establishment and define the network of molecular interactions involved in EGF/Hh cytoneme-mediated signaling crosstalk during Drosophila development, to finally experimentally test application in a Human cancer cell model. The work will not only yield understanding of fundamental mechanisms for cytoneme-mediated signalling, but will identify the role of signal pathway crosstalk in multicellular living systems, allowing translation of this fundamental developmental biology to the field of applied biomedical science.

Resumen del Currículum Vitae:

I am a cell and molecular biologist interested in the molecular and structural mechanisms for inter-cellular communication during development and disease. I graduated in my original country, Mexico, with great aspirations to carry out postgraduate biomolecular research. This determination led me to apply for funding to come to Europe and achieve a PhD, being awarded a five year scholarship for outstanding graduates from the University of Guadalajara, Mexico.

During my PhD and first postdoctoral position, I studied the function of the ubiquitin ligase Ariadne-1a in the regulation of hormone signalling during development, and its consequences in neurodegeneration. Particularly, I discovered the role of regulated protein degradation through ubiquitination in the specification of the cellular response to the hormonal signal ecdysone, an essential process in the organization and development of Drosophila tissues. This work led to my first research publication (Gradilla et al Genetics 2011) and initiated my great interest in the study of the mechanisms for the organization of multi-cellular organisms, and specifically how cells communicate with each other at a distance during development and in relation to disease scenarios.

After this period I had a career break of three years due to the birth and care of my two children, now aged 5 and 7. However, I was determined to return to my research interest, and despite the difficulties for re-entering an academic career I was able to obtain a research associate position as part of a Marie Curie Training and Mobility of Researchers network. During this second period of active research (two and a half years) I have produced three major research papers (Gradilla et al, Nat Comm 2014, Bischoff, Gradilla et al, Nat Cell Biol 2013, Bilioni et al Dev Biol 2013) and written two review papers, demonstrating my capacity as a researcher with an already high level of independence, and a research area at the forefront of advances in molecular biology. Specifically, I investigated the role of filopodia-like membrane protrusions or cytonemes and exovesicle release in the controlled signalling of the morphogen Hedgehog during

development.

Since 2013, based at the University of Exeter (UK), I have developed an independent research project with great potential for making important advances in pure and applied biology, with considerable scope to act as the springboard to a successful career in research. This proposal is anchored in my latest research and allied directly with my main interests as a scientist, but is focused on an untested yet fundamental area of molecular cell biology. In the next five years I aim to develop research on mechanisms for cytoneme establishment and cell to cell communication, combining genetic molecular and cell biology tools, as well as exploring potential application to a mammalian cancer model. In addition I also plan to develop research on the involvement of these cytoskeleton structures during crosstalk of signalling pathways in development and disease. A Ramon y Cajal Fellowship funding my proposal would undoubtedly allow me to pursue my career goals as well as contribute to the understanding of how cells behave in a multicellular context during development and in a cancer scenario.