Science and Technology Group
Annual Report FY2015

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1 Introduction

My area of interest is in the behavior of receptors within the cell membrane, specifically the epidermal growth factor receptor. During the 2015 financial year I have been investigating the mechanism of activation of the epidermal growth factor receptor using total internal reflection (TIRF) microscopy and single molecule tracking algorithms. This work has been done in collaboration with Prof. Sir Walter Bodmer at the Weatherall Institute of Molecular Medicine, University of Oxford, UK, Prof. Mark Leake at the University of York and Dr. Isabel Llorente Garcia, University College London, UK.

2 Activities and Findings

Many proteins within the cell membrane are receptors. Receptors collect signals, usually in the form of a small protein molecule, from outside the cell and transmit the signal inside the cell.

Two different mechanisms for transmitting the signal from the outside to the inside of the cell have been proposed for the epidermal growth factor receptor. The first model is inspired by the crystal structures of the extracellular domain and is called the dimerization model. Here the receptor exists as a monomer on the surface of the cell. The ligand binds to this receptor monomer inducing a conformational change that allows two ligand bound receptor monomers to come together to form a dimeric complex. This leads to activation of the both receptors tyrosine kinase domains and transmission of the signal inside the cell. The second model is based on fluorescence microscopy imaging of the receptor and receptor-ligand binding studies and is called the rotational model. Here the receptors exist constitutively in a dimeric complex and the ligand binds to one of these receptors leading to rotation of the transmembrane domain, activation of the tyrosine kinase domain and transmission of the signal to the inside of the cell.

We have been investigating these two models of activation using the epidermal growth factor receptor tagged with green fluorescent protein and its ligand, epidermal growth factor receptor tagged with tetramethylrhodamine. These fluorescently tagged receptors and ligands have been visualized in live colorectal carcinoma cells with TIRF microscopy and an algorithm for identifying locations and tracking movements of these receptors and ligands has been developed.

Using these techniques we can determine how the receptors are arranged on the surface of the cell before and after ligand binding. We find that the epidermal growth factor receptor in usually located within a complex of receptors of varying sizes rather than as monomeric receptor, which supports the rotational model of activation, and after ligand binding the ligand-bound receptors cluster together into much larger complexes before being internalized.

3 Collaborations

Theme: Mechanism of Activation of the Epidermal Growth Factor Receptor.

Type of Collaboration: Joint Research

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Researchers:

- Dr. Charlotte Fournier,
  Okinawa Institute of Science and Technology, Japan.
- Prof. Sir Walter Bodmer,
  Weatherall Institute of Molecular Medicine, University of Oxford, UK.
- Prof. Mark Leake,
  University of York, UK.
- Dr. Isabel Llorente-Garcia, University College London, UK.

4 Publications and other output

Nothing to report.