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EGFR TRAFFICKING AND SIGNALLING: INSIGHTS FROM MATHEMATICAL MODELLING

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One of the most important tyrosine kinase receptors, mediating signals for proliferation, differentiation and development is the epidermal growth factor receptor (EGFR). Human cancer is often characterized by dysfunctional EGFR signalling induced by the overexpression of the receptor and/or the upregulation of its ligands. The EGFR fate and signalling are regulated by several mechanisms of which the major is the endocytosis. EGFR can be internalized through two internalization pathways depending on the ligand dose, *i.e.*, the clathrin-mediated endocytosis (CME) and the non-clathrin endocytosis (NCE). They regulate the recycling or degradation fate of the receptors. Particularly, NCE is related to EGFR degradation whereas CME is mainly linked to receptor recycling and sustained signalling, see Figure 1.

In this contribution, preliminary results will be provided on the development of a novel mathematical model of EGFR trafficking to test hypotheses on the principal mechanisms regulating the different EGFR endocytosis pathways and their impact on EGFR signalling propagation. The extended dynamical model is built starting from an early activation model (EAM) [1], consisting of a system of ordinary differential equations (ODEs), focusing on the first two minutes after EGF stimulation. The extended model herein presented fits *ad hoc* data from wet-lab experiments and provides a more accurate quantitative description of the EGFR phosphorylation and ubiquitination processes. Moreover, it includes for the first time a preliminary description of the EGFR internalization processes. The current model allows simulating the system for longer time periods and provides a unique opportunity for building a computational framework to investigate how EGFR signalling/endocytosis dysfunction could contribute to the tumorigenic process.

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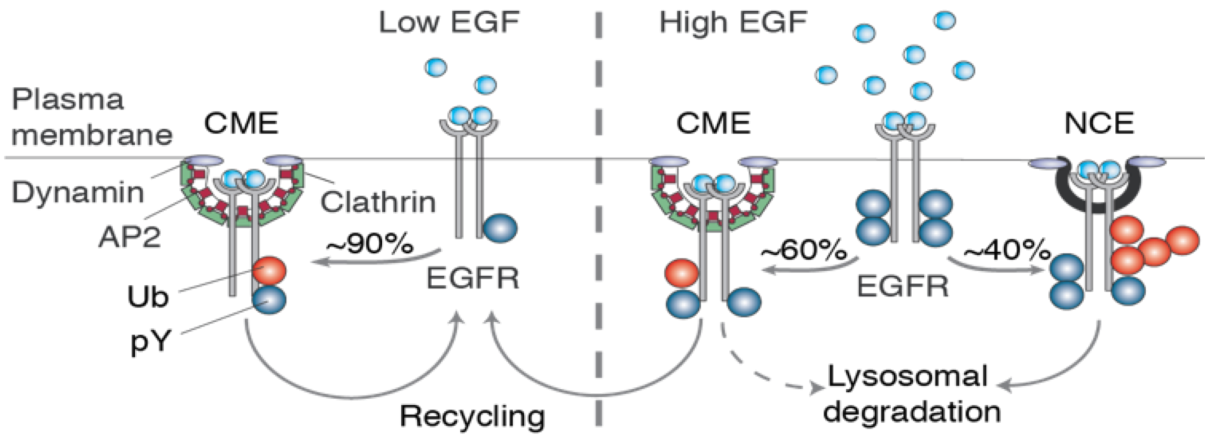

Figure 1: EGFR is internalized either via CME or NCE: CME is activated at low EGF doses and it is mainly involved in EGFR recycling and sustaining signalling; the NCE is activated only at high EGF concentrations, and it leads primarily to receptor degradation and signals extinction, representing a mechanism to protect cells from overstimulation.

References

[1] Capuani, F., Conte, A., Argenzio, E., Marchetti, L., Priami, C., Polo, S., Di Fiore, P.P., Sigismund, S., & Ciliberto, A. (2015). *Quantitative analysis reveals how EGFR activation and downregulation are coupled in normal but not in cancer cells*. Nature Communication, 6, 7999. https://doi.org/10.1038/ncomms8999

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