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Commentary Open Access

Shaping ERBB Signalling by Steroid Hormones

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Commentary

The Epidermal Growth Factor Receptor (EGFR) was the first member of ERBB receptor discovered, which was found to be directly mutated in human cancer [1]. It belongs to the Receptor Tyrosine Kinase (RTK) superfamily, which counts at least 58 members subdivided in several classes. RTKs are transmembrane proteins sharing two major functional domains: the extracellular ligand-binding domain and the intracellular tyrosine kinase domain that distinguishes them from all other receptors. RTKs are activated via ligand-induced dimerization (for example, EGFR) or allosteric transitions (insulin receptor) that results in activation of the intrinsic tyrosine kinase and trans-phosphorylation of the cytoplasmic domain, creating docking sites for phosphotyrosine-binding effectors that initiate intracellular signalling cascades [2].

Members of the RTK family play pivotal roles in a multitude of physiological processes during development and adult life. Malfunction of RTK signalling is a leading cause of major human diseases, ranging from developmental defects to chronic inflammatory syndromes, diabetes and cancer. Indeed RTKs represent widely intercepted targets for cancer treatments, for example targeting of ERBB2 and EGFR/ERBB1 represents one of the most promising treatments for breast and colon cancers [3].

Early studies supported the idea of a linear and vertical transmission of EGFR signalling, which appeared to be propagated downstream through multiple effectors. Nevertheless, in the last decade, the development of high-throughput technologies uncovered ERBB family as a signalling network following the principles of network theories, characterized by both stability and robustness. The stability is guaranteed by the presence of multiple levels of regulatory loops, such as feed-back and feed-forward loops [4,5]. Integrated and often intertwining negative- and positive-feedback circuits help to maintain appropriate quantitative and dynamic relationships between inputs (growth factor stimuli) and outputs (cellular response). This ensures that most cellular parameters stay under tight control within a narrow range and around a certain optimal level. For this reason, feedback deregulation is often responsible for diseases. On the other hand, robustness relies on the property of few proteins to interact with multiple molecular players, so that the blockage of one of these arms can be easily bypassed by alternative routes. These proteins represent bona fide "hubs" of the network. Obviously, the identification of networking hubs as well as modulators of feedback systems is critical for understanding signal dynamics, either in physiological or pathological conditions. Furthermore, the fine-tuning of these pathways might allow the optimal selection of targets for therapeutic purposes.

By global and time-resolved analysis of transcriptional response, we investigated the crosstalk between the growth factor EGF and the glucocorticoid receptor (GR), a member of the steroid hormone receptor family. Steroid hormone receptors, which belong to the nuclear receptor (NR) superfamily, reside and get activated directly in the intracellular space, due to the lipophilic nature of their ligands. We unveiled that GR mediates a robust control of EGFR signalling by both massive repression of EGFR positive feedback loops (such as ligands) and simultaneous production of EGFR negative feedback loops (such as deactivators of signalling players) [6]. This unveiled genomic interaction introduces GR into the EGFR biological network, adding a layer of complexity to the ERBB pathway. In particular GR displays a high level of connectivity with transcription factors downstream to EGFR, thus controlling EGFR transcriptional response. Therefore GR represents an important hub of ERBB transcriptional network, strongly impacting on the stability of ERBB network by modulating its own feedback production machinery. Importantly, this might translate into fragility of the ERBB network, since deregulation of GR activity might impair the stability of ERBB pathway. On the other hand, these findings may be easily translated into therapeutic purposes, since GR activity can be easily actioned and exogenously manipulated in vivo by administration of specific positive or negative modulators.

So far extensive studies steered the role of steroid hormones and ERBB pathways individually. However, as we recently reviewed [7], a careful analysis of data available in the literature supports an extensive interconnection between steroid hormones and ERBBs, which may even extend to the bigger RTK and NR superfamilies. The existence of this crosstalk is supported by the evidence that all steroid hormones regulate overlapping molecular cascades to ERBBs (and RTKs). Further, several evidences suggest that all steroid hormones play a fundamental role in shaping growth factor-induced signalling and outcome by their intrinsic ability to simultaneously regulate positive and negative regulatory feedback loops, either in a positive or in a negative way, at both genomic and non-genomic levels (Figure 1). Finally, the overall observation that ERBB signalling modulates the expression levels and activity of certain steroid hormone receptors, which in turn regulate ERBB expression levels and signalling, suggests

that steroid hormone receptors themselves might be part of the ERBB feedback machinery, connecting peripheral tissues to systemic cues dependent on steroid hormone release.

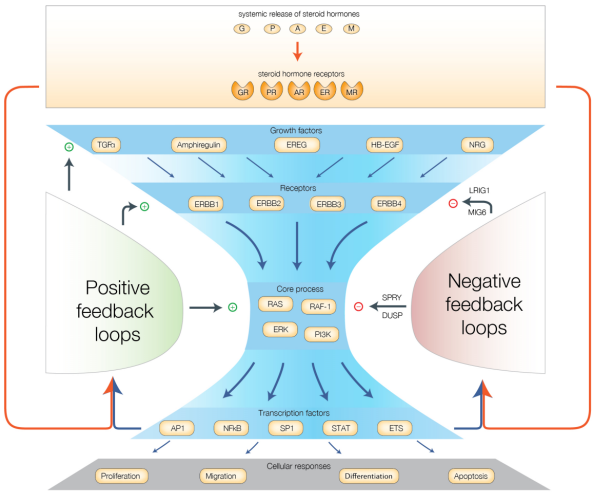

Figure 1: Positive and negative regulatory feedback loops.

We think that deeper understanding of crosstalk between steroid hormones and ERBB receptors is critical in order to dissect the complexity of biological processes, including development, circadian rhythms, tissue renewal and regeneration and pathological conditions, such as cancer. The existence of such interactions extends the current methods to modulate ERBB signalling in vivo, in specific responsive tissues. For example, for regenerative purposes, steroid hormones administration may be able to boost ERBB2 signalling in order to trigger cardiac regeneration following injury [8].

System-based and advanced technologies for the analysis of the interactions between steroid hormones and ERBBs may lead to major advancements in molecular medicine, providing the basis for new routes of pharmacological intervention in several diseases, including cancer.

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