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Receptor Tyrosine Kinase KIT: A New Look for an Old Receptor

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Receptor tyrosine kinases (RTKs) control various signalling pathways in cells. Their remarkable conformational plasticity enables the specific recognition of many molecules such as ligands, substrates or proteins. In solution, RTKs are in equilibrium between different conformations ranging from an inactive auto-inhibited state to a fully active state. Ligand-induced activation of RTKs leads to the recruitment and activation of multiple downstream signalling proteins carrying the signal to the nucleus, where it alters the transcription patterns of genes that govern various aspects of cell physiology [1]. The explicit elucidation of signalling events is an important and unresolved problem in cell biology. The initiation of these cascade-like processes involves different domains of RTK, each of them performs its own specific actions, which are finely concerted by a tightly regulated allosteric mechanism that controls all functional processes [2]. Aberrant regulation of RTKs signalling networks is associated with the progression of many diseases.

Focusing on the RTK KIT, an important target in oncology (leukaemia, mastocytosis, melanoma, gastrointestinal stromal tumour, and stomach cancers) [3], we first explain its physiological and mutation-induced activation [4]. Next, we will discuss KIT as a key starter/regulator of intracellular signalling which is mediated by regions possessing multiple phosphorylation sites. Since these regions are very flexible or disordered, they are not well understood yet. We present the first structural model of the full-length cytoplasmic domain of KIT, which contains all regions involved in post-transduction processes, phosphorylation and binding of intracellular protein [5] (Figure 1).

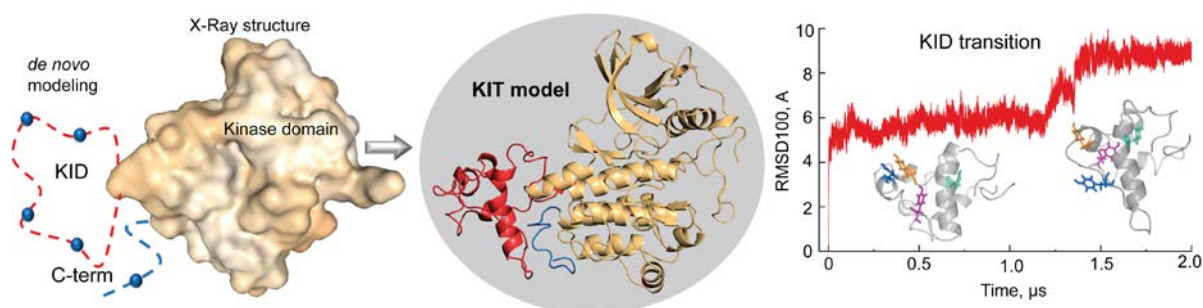


Figure 1. Modelling of the cytoplasmic domain of the RTK KIT. *Ab initio* models of KID and C-term were integrated into the X-ray structure (left); the KIT model (middle) with kinase domain (yellow), KID (red) and C-terminal (blue) was refined by molecular dynamics simulation. The KID conformational transition (right) is illustrated by RMSDs and two conformations selected before and after the transition (at $t = 0.8$ and $2 \mu\text{s}$).

Rigorous analysis of the structure and dynamics of KIT, carried out using advanced mathematical methods, has led to a new vision of KIT as a multidomain protein made up of structurally ordered and disordered regions which together constitute a mutually and tightly

driven engine [6,7]. This atomistic model of an allosterically regulated KIT is the first step for the reconstruction of its INTERACTOME, which consists of a set of KIT complexes with its signalling proteins, and DYNASOME, which constitutes an ensemble of intermediate conformations of KIT before, over and after the post-transduction processes. The practical delivery of such modelling consists in defining targets for the development of modulators/inhibitors capable of regulating or blocking several steps of KIT activation or its post-transduction processes in cells.

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