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Activation mechanism of Parkinson's Disease-associated LRRK2 in *Dictyostelium*

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Introduction

Mutations in leucine-rich-repeat kinase 2 (LRRK2) are thus far the most frequent cause of late-onset **Parkinson's Disease** (PD). LRRK2 belongs to the **Roco family** of proteins, which are characterized by the presence of a Ras-like G-domain, called **Roc**, a dimerization domain, called **COR**, and a **kinase** domain. PD mutations spread all over the protein result in decreased GTPase activity and enhanced kinase activity, suggesting a possible PD-related **gain of abnormal function**. Interestingly, mutations in the Roc GTPase domain also influence kinase activity and *vice versa*, pointing towards a **cross-talk between the domains**.

Key questions:

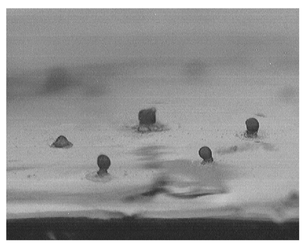
How is protein activity regulated?

What are the fundamental defects in Parkinson mutants?

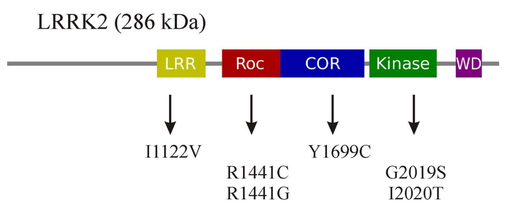
What is the 3D structure of the protein?

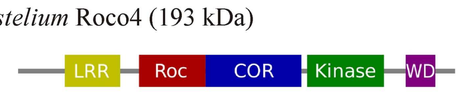
Inhibitors and therapeutic targets?

Human patient
(Gowers, 1886)

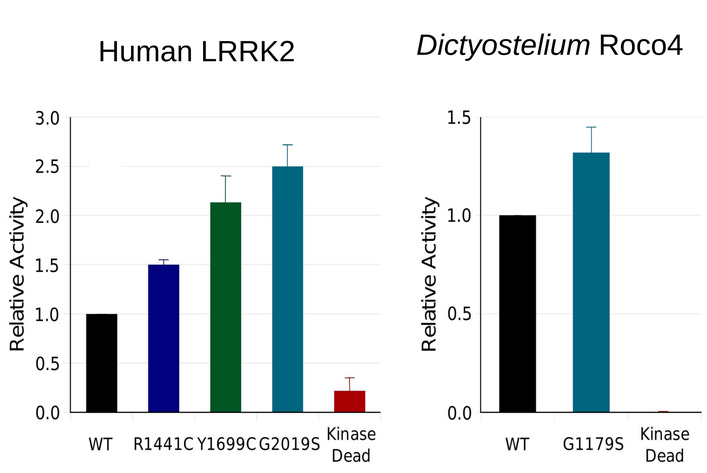


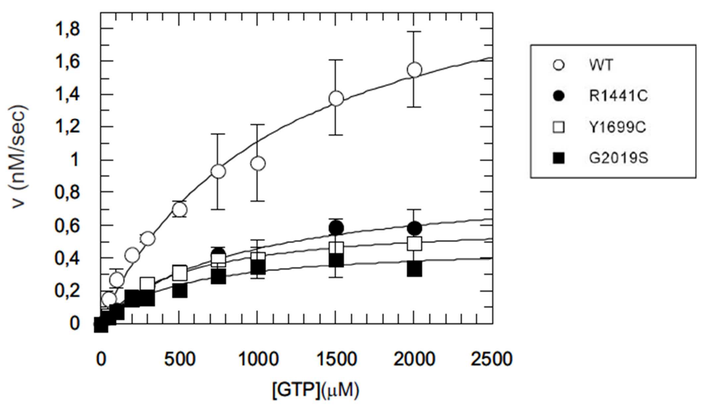
Dictyostelium 'patient' *roco4*-null



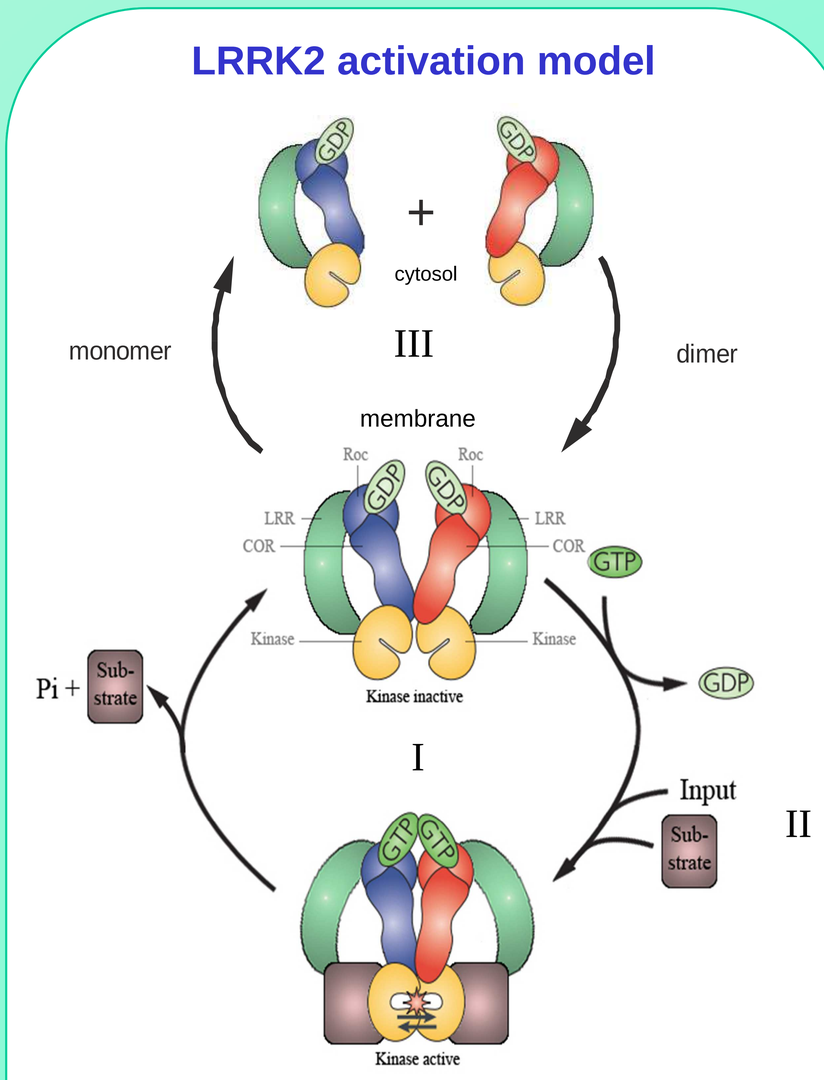


Parkinson protein is hyperactive





LRRK2 activation model



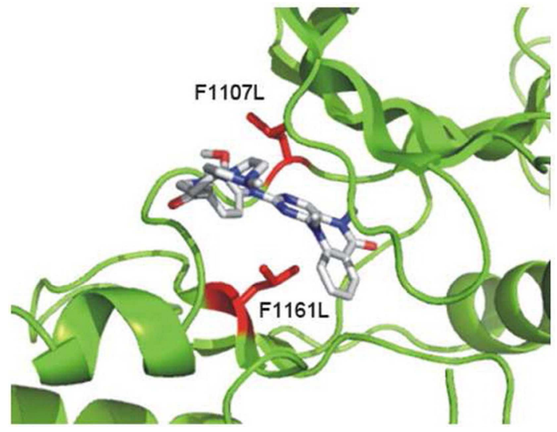
Regulation mechanisms:

I Intra-molecular regulation

II Inter-molecular regulation (input / substrate)

III Dimerization and translocation

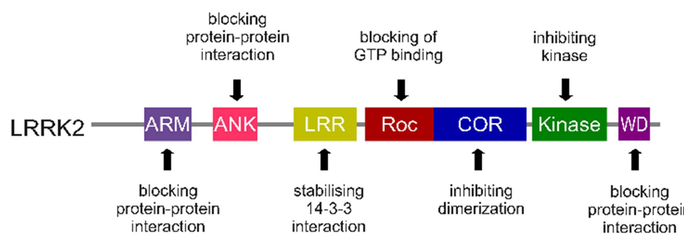
Therapeutics



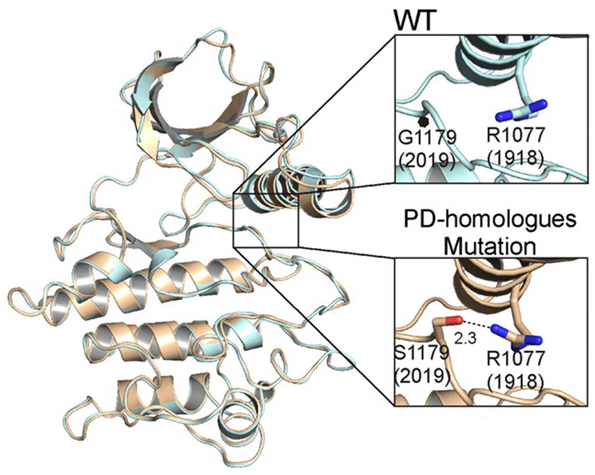
Structure of the kinase inhibitor LRRK2-IN-1 bound to a humanized (red) Dictyostelium Roco kinase

LRRK2 kinase inhibitors have been developed, but almost all show lethal side effects.

Therefore, alternative approaches that target other domains of LRRK2, preventing dimerization or leading to allosteric modulation of the kinase domain, may have significantly improved therapeutic benefits.



One Hydrogen bond makes the difference



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