

# Cell Biology of the Phosphor-tyrosine Signaling Pathway of CED-1

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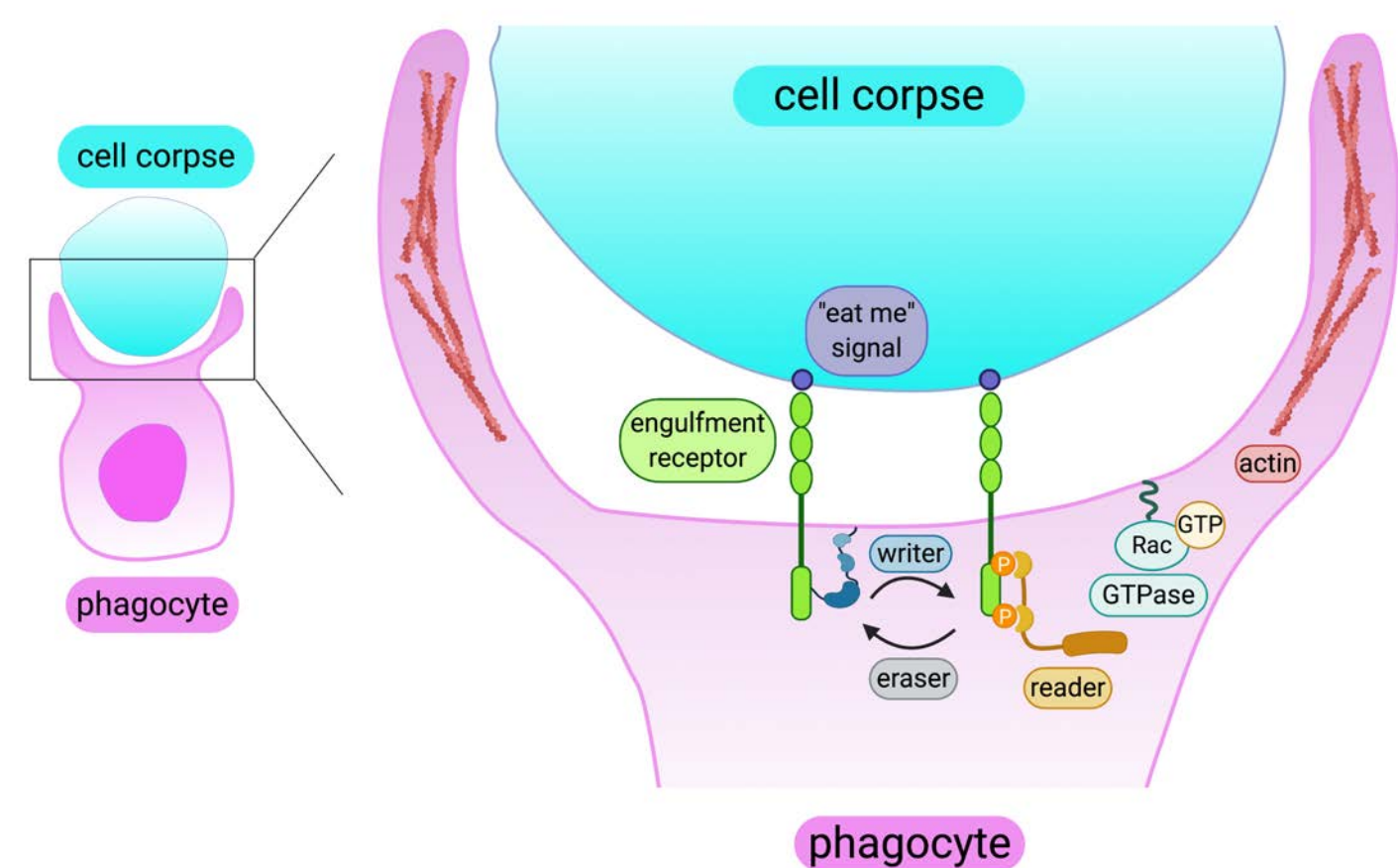
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## Abstract

Phagocytosis is a process in which cell corpses are cleared by engulfing cells. In *C. elegans*, *Drosophila melanogaster*, and mice, homologous scavenger receptors of cell death abnormal-1 (CED-1), Draper, and MerTK and MEGF10, respectively, complete this process. A literature review of the conserved and underlying cell biology of all 4 receptors was sorted and read. Here, the learned *ced-1* cell biology in association with *ced-6* and *ced-7* extracted from published works is reported as well as the application of the writer, reader, eraser (WRE) of the phosphor tyrosine signaling framework credited by Lim and Pawson (2010). In this, the WRE are protein kinases, ITAM recognizers, and phosphatases, accordingly. Upon literature analysis, the process of CED-1 ligation is well understood but additional cell biology studies are required in order to properly utilized the WRE framework.

## Ancestral Figure

Engulfment signaling modules used by phagocytes across phyla



## Methods

To conduct this research, we used PubMed as the online database to find published scientific and review articles related to worms and *ced-1*. Additionally, Web of Science was also used to find citations of relevant articles. After methodically sorting all applicable abstracts and reading important papers, drafts of the known *ced-1*, *ced-6*, *ced-7* pathway cell biology were submitted and revised.

## Results

Cell engulfment is initiated when neighboring cells of cell corpses release a secretory protein called Transthyretin-related 52 (TTR-52) family domain to mediate the recognition of phosphatidylserine (PtdSer) to CED-1.<sup>1</sup> CED-7, a homolog protein of the mammalian APT Binding Cassette (ABC) transporter, enables the presentation of PtdSer molecules to the surface of the cell corpse.

Furthermore, CED-1 is a transmembrane protein that has an extracellular region composed of EMI and EGF-like domains which interact with TTR-52 and PtdSer. Its cytoplasmic region contains a tyrosine phosphorylation site of YXXL.<sup>2,3</sup> The tail also contains an NPXY motif with tyrosine residues which might be auto-phosphorylated upon receptor ligation.<sup>4</sup> Furthermore, YXXL motif contains a possible site for phosphor tyrosine kinase (PTK) phosphorylation and SH2 domain binding while the NPXY motif contains a possible site for Phosphor-Tyrosine Binding (PTB) interaction.<sup>2</sup>

Lastly, CED-6 is an adaptor protein that functions downstream of CED-1. It physically binds to an activated NPXY motif which leads to an association with GTPase CED-10/Rac. CED-10 is responsible for directing actin remodeling and serves as a converging factor in both cell clearing pathways.<sup>5</sup> A secondary outcome of this interaction is recruitment of DYN-1 to facilitate vesicle aggregation at the phagocytic cup and phagosomes.<sup>6</sup>

An alternative hypothesis is that CED-1/CED-6 interaction causes the recruitment of adapter protein EPN-1 which eventually recruits clathrin.<sup>7</sup> The heavy chain (CHC-1) and AP-2 subunit of clathrin along with EPN-1 form a protein complex that interacts with CED-6, leading to actin rearrangement at the phagocytic cup.<sup>8</sup> In this, the CED-1/CED-6; EPN-1; clathrin pathway operates independent of the *ced-10*/Rac GTPase pathway.

## Discussion

This analysis is sequenced with an application of the WRE framework. In review of the published *ced-1* research, there is no mention of PTKs (protein tyrosine kinases) used to activate the tyrosine residues on the cytoplasmic region of CED-1. Notably, the NPXYL motif does not require PTKs for activation. The activation of these motifs leads to recruitment of an unspecified SH2 molecule to YXXL and physical interaction of CED-6 with the NPXY motif. The SH2 molecule and CED-6 are considered readers of the tyrosine signal though how they're recruited to this site is currently unexplained in *ced-1* literature.

As for erasers, the main candidate is retromer which as been studied and identified in sorting and recycling CED-1 once phagosome maturation begins.<sup>9</sup> Retromer remains a strong contender of an indirect tyrosine signal eraser in this engulfment pathway.

## Figures

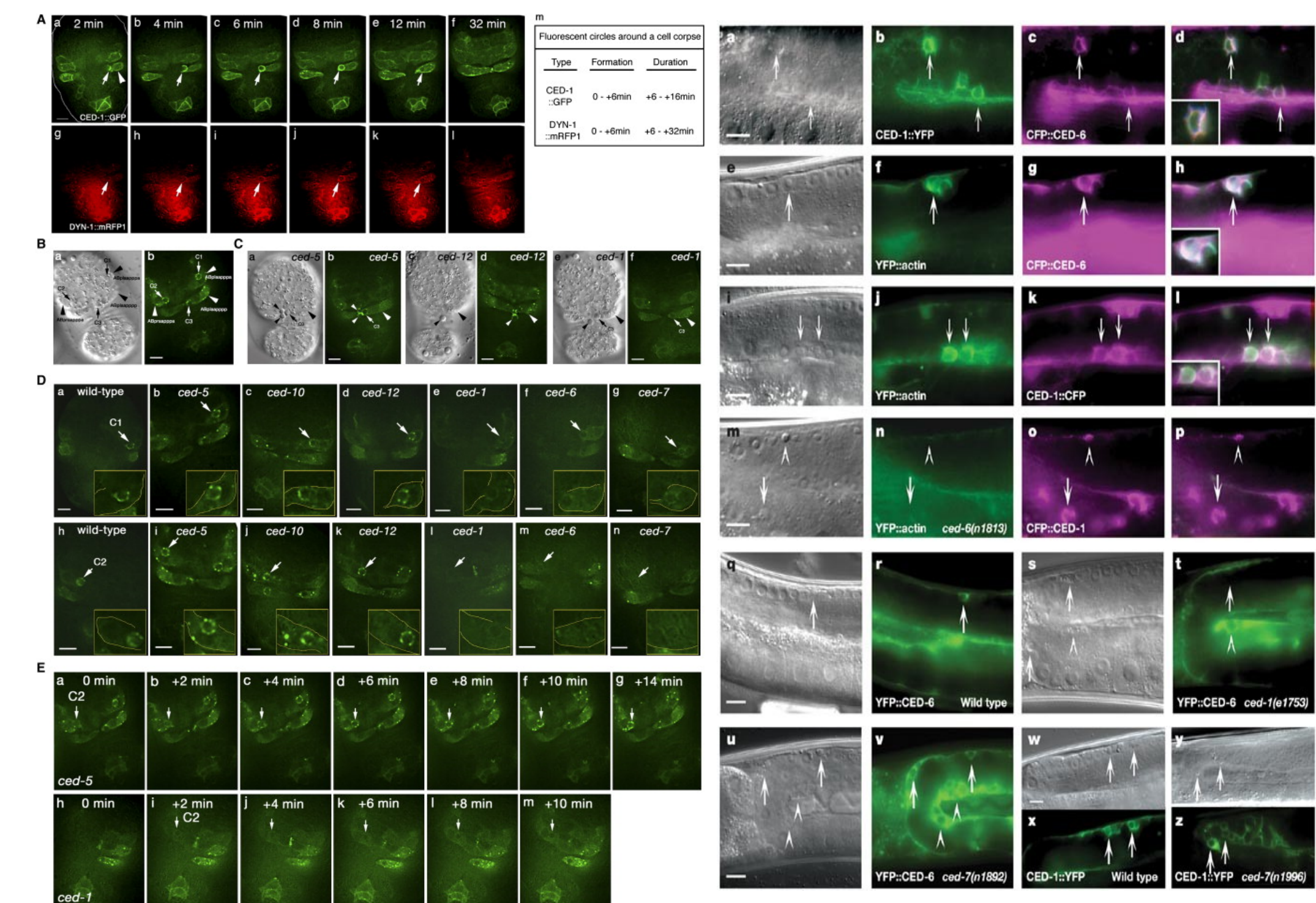


Figure 5, Yu et al. 2006  
Recruitment of DYN-1

Figure 2, Kinchen et al. 2005  
Actin recruited to phagocytic cup

## Conclusions

Within the *ced-1*, *ced-6*, and *ced-7* gene pathway, a significant amount of information is understood on how engulfment is initiated and the proteins required. Nonetheless, the kinases required to activate the tyrosine residue on the cytoplasmic region of CED-1 and the exact cell biology of CED-6 downstream of CED-1 stands for further investigation. Conducting such research work in perspective to the WRE framework not only redefines how phagocytic receptors are viewed, but also it can be used to generate therapeutic research through cell engineering.

## References

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