The heat shock protein LarA activates the Lon protease in response to proteotoxic stress

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The Lon protease is an ATP-dependent protease that is highly conserved in cells of all tree domains of life[1]. It has important roles in both regulation and protein quality control[1–4]. The Lon protease has associated in mammalia to ageing, neurodegenerative diseases and cancer[5], while it affects a wide range of cellular processes like cell cycle progression, cell differentiation and stress response in bacteria[6]. In order to identify interactors of the Lon protease in the fresh water bacterium *Caulobacter crescentus* we used a proteolytically inactive variant of the Lon protease to set up a protease trapping approach[7]. Thereby, we discovered a conserved α-proteobacterial heat shock protein, LarA. We found that elevated levels of LarA lead to a Lon-dependent growth inhibition and that LarA temporarily accumulates after the onset of proteotoxic conditions such as heat stress. Eventually, pre-stress levels of LarA are restored by Lon-dependent degradation of LarA itself. Furthermore, we showed that LarA stimulates the degradation of a variety of substrates of the Lon protease in an allosteric manner. In detail characterization of LarA-dependent stimulation showed that the ultimate 5 amino acids of the C-terminus are crucial for its activating properties as well as degradation of LarA by Lon. Based on our findings, we suggest that induction of LarA during early phases of proteotoxic stress helps to meet the elevated proteolytic demand caused by protein unfolding stress. Later during stress adaptation or during recovery after stress, degradation of LarA by the Lon protease prevents detrimental effects caused by excessive proteolytic activity.

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