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Minireview

Pseudomonas fluorescens orchestrates a fine metabolic-balancing act to counter aluminium toxicity

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Summary

Aluminium (Al), an environmental toxin, is known to disrupt cellular functions by perturbing iron (Fe) homeostasis. However, Fe is essential for such metabolic processes as the tricarboxylic acid (TCA) cycle and oxidative phosphorylation, the two pivotal networks that mediate ATP production during aerobiosis. To counter the Fe conundrum induced by Al toxicity, *Pseudomonas fluorescens* utilizes isocitrate lyase and isocitrate dehydrogenase-NADP dependent to metabolize citrate when confronted with an ineffective aconitase provoked by Al stress. By invoking fumarase C, a hydratase devoid of Fe, this microbe is able to generate essential metabolites. To com pensate for the severely diminished enzymes like Complex I, Complex II and Complex IV, the upregulation of a H_2O-generating NADH oxidase enables the metabolism of citrate, the sole carbon source via a modified TCA cycle. The overexpression of succinyl-CoA synthetase affords an effective route to ATP production by substrate-level phosphorylation in the absence of O_2. This fine metabolic balance enables *P. fluorescens* to survive the dearth of bioavailable Fe triggered by an Al environment, a feature that may have potential applications in bioremediation technologies.

Al toxicity and impact on essential metal nutrients

Although Al is the most widespread metal in the earth's crust, it is not known to be involved in any biological function yet (Soni *et al.*, 2001). Thus, it seems that organisms may have deliberately circumvented the incorporation of this metallic element during evolution. This is not surprising as Al interferes with a variety of biological processes due to its ability to mimic numerous essential cellular metals such as Fe, Ca and Mg. Ca^{2+}-mediated signalling pathways are markedly perturbed by Al (Mundy *et al.*, 1997). In trace concentrations, this trivalent metal has been shown to interfere with the protein kinase C-mediated pathways (Quarles *et al.*, 1994), cAMP homeostasis (Hartle *et al.*, 1996) and glutamate-nitric oxide synthase-cGMP signalling network (Lajeunesse *et al.*, 1998). ATP stabilization and membrane dynamics catalysed by Mg is also known to be affected by Al (Nayak, 2002). This interference in the homeostasis of these two essential divalent metals has severe implications on cellular metabolism.

Such Al-triggered perturbations of living systems have become a concern due to the enhanced bioavailability of this trivalent metal (Yokel and McNamara, 2001). Industrial pollution coupled with the widespread use of Al in a variety of consumer and medical products have indeed made this toxin a public health threat. Although the exact molecular details responsible for the toxicity of Al still need to be delineated, its involvement in a variety of diseases has been documented. We have recently shown how Al toxicity leads to enhanced lipid production and accumulation in hepatocytes, liver cells responsible for a variety of metabolic processes (Mailloux *et al.*, 2006). Its ability to perturb cellular morphology in astrocytes has also been demonstrated (Lemire *et al.*, 2009). These cells are critical for the proper functioning of the brain. This is important as the star-shaped astrocytes are essential for normal cerebral functions. The inability of astrocytes to interact with neurons due to Al toxicity may be a cause to various neurological abnormalities associated with Al (Nayak, 2002).

Al interferes with Fe homeostasis

As Al and Fe share numerous common physicochemical features, it is not surprising that Fe metabolism is severely affected during Al stress (Morgan and Redgrave, 1998). Al is known to impede proteins/enzymes that are dependent on Fe to function in an effective manner due to their

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