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Crossing the mitochondrial barrier *in vivo*: RNA modulates degeneration to regeneration through mitochondrial restoration

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Mitochondrial dysfunctions are believed to play a critical role in variety of human diseases. Mitochondrial disorders principally affect tissue with high ATP turnover, such as muscle and brain. An effective and efficient method of nucleic acid delivery to mitochondria in vivo is lacking. Earlier we have observed that a multiprotein RNA transport complex (RIC) derived from a protozoal parasite is able to deliver large polycistronic (pc) RNAs encoding the H-strand of rat mitochondrial genome to the mitochondria of animal tissues in vivo. By in vivo imaging we could monitor the bioavailability of injected RNA in muscle and other tissues in real time. Lentiviral shRNA mediated knockdown showed that uptake of the RNA in muscle was dependent on caveolin-3, but not on caveolin-1 or clathrin (HC) indicating an endocytic mechanism. pcRNAs were rapidly taken up into mitochondria and underwent processing to generate translatable mRNAs restoring translation and the respiratory capacity of the muscle, especially in middle aged (14month old) rat .The effect on older(26month) rats was moderate; this was reflected by defective RNA processing and reduced translation efficiency in aged mitochondria. We further showed that a combination of pcRNAs spanning the mitochondrial genome restored mitochondrial function Increased Intramuscular ATP levels as well as respiration and reduced reactive oxygen species in injured rat muscle. These effects combined to produce a notable increase in the rate of wound resolution, accompanied by reduction of fibrosis resulting in marked acceleration of myogenesis and vasculogenesis and improvement of muscle contractile function. There was evidence of proliferation of Pax7 satellite cells, and that they were sensitive to mitochondrial inhibitors, indicates the importance of oxidative phosphorylation. These results highlight the activation of endogenous stem cells through mitochondrial restoration as a possible alternative to implantation of cultured stem cells.

Biography

Sukanta Jash is currently a senior research fellow under –CSIR, Govt of India and submitted his PhD thesis. After completion of his Masters in Science with distinction he cleared two top national level examinations for PhD conducted by CSIR- Govt of India, and then he joined as junior research fellow in Dr Samit Adhya's laboratory in IICB and started working on mitochondrial RNA therapy and contributed significantly in mitochondrial gene therapy. He has published 5 papers in reputed international journals. He is currently working on the signalling crosstalk that regulates microenvironment of muscle stem cells in RNA induced acceleration of muscle regeneration.

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