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Induction of pro-healing macrophages through the reprogramming of invading monocytes: A new antirestenotic strategy

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Introduction: Monocyte-derived macrophages are implicated in inflammatory reactions characteristic of restenosis after angioplasty and/or stent implantation. Since the role of macrophage-mediated chronic inflammation in the progression of restenosis is well-established, multiple approaches have been devised to decrease the number and/or functionality of mononuclear phagocytic cells residing in angioplastied and stented arteries. However, no prior research has exploited the capability of monocytes to target sites of vascular injury in order to introduce pro-healing "therapeutic" genes into diseased vasculature. Here we report preliminary results demonstrating the feasibility of this concept.

Methods and Results: Monocytes were isolated from heparinized rat blood by sequential Ficoll gradient centrifugation and negative selection with immunomagnetic techniques. 5x105 cells fluorescently labeled monocytes were administered via tail vein to rats that underwent balloon denudation injury of carotid arteries 4 days prior to cell therapy. The labeled cells were observed both in the nascent neointima and in the adventitia of balloon-injured arteries of rats sacrificed 4 days after cell therapy (8 days after balloon injury). The labeled cells unvaryingly carried CD68 pan-macrophage marker as assessed by immunofluorescence analysis, and comprised 30% of total macrophages in the neointimal tissue of rats treated with ex vivo modified monocytes. To verify functional competence of adoptively transferred monocytes, isolated monocytes were transduced with adenoviral vectors encoding firefly luciferase and were administered to rats that underwent Fogarty balloon injury 4 days prior to the cell delivery. One and 4 daysafter cell delivery, luciferase expression in balloon injured arteries was confirmed by bioluminescence imaging. Furthermore, monocytes exogenously transduced with adenovector driving expression of adiponectin, an M2-macrophage inductive factor, were capable of reducing neointimal hyperplasia in balloon injured carotid arteries upon systemic administration to rats 2 days after balloon injury.

Conclusions: These pilot studies demonstrate the feasibility of using ex vivo transfected autologous or syngeneic monocytes as a means to introduce pro-healing factors to angioplastied and/or stented vasculature with the aim of restenosis mitigation.

Biography

Ilia Fishbein received an MD degree from the University of Saratov (Russia) in 1987. He completed his PhD studies on polymeric delivery systems for the prevention of restenosis at the Hebrew University of Jerusalem (Israel) in 2000. His Postdoctoral research at the Children's Hospital of Philadelphia (USA) has been concerned with vascular gene therapy and substrate-mediated delivery systems of viral vectors to diseased vasculature. He is an Assistant Professor at the University of Pennsylvania. His current work is related to gene-eluting stents and pharmacological modulation of vascular gene therapy for the prevention of restenosis.

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