CD36 is required to prime cardiomyocytes to proliferation

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Many approaches have been explored to regenerate the heart muscle following ischemic injury, out of which is the induction of cardiomyocytes proliferation. Our previous work demonstrated that cell-cycle was successfully induced in cardiomyocytes by viral expression of combination of four cell cycle factors: cyclin B1, CDK1, cyclin D1 and CDK4; termed as 4 factors (4F). However, only 15-20 % of the cells expressing the four factors progress into cell-cycle, while the remainder are quiescent. A pertinent question in the field of cardiac regeneration is why all viral or in vivo transgenic approaches to induce adult cardiomyocyte proliferation, e.g., 4F, YAP, and CyclinA2, promote proliferation in only a subset of cardiomyocytes. This general finding suggests that factors or conditions beyond cell cycle induction influence the probability and perpetuation of cardiomyocyte division.

Here we aim to investigate why only a subpopulation of cardiomyocytes is able to progress through cell cycle.

 Temporal single cell RNA sequencing of 60 day mature hiPS-CMs 24, 48 and 72 hours post infection with 4F or control virus revealed that a unique population of cardiomyocytes in the LacZ control group [1026 cells out of 6761 cells (~15%)] that disappears after treatment with 4F; another unique cluster with similar cell numbers appears 24 h after 4F transduction (Cluster 3), which suggests that the initial population was primed to proliferate. One of the major characteristics of this primed subpopulation is the expression of CD36, a major fatty acids transporter in cardiomyocytes, and that 4F induction of cell-cycle completely abolish CD36 expression. knocking down CD36 in hiPS-CMs for 48 hours followed by induction of proliferation using 4F led to 50-70% reduction in proliferation capacity of the cardiomyocytes compared to the control cells. Furthermore, cardiomyocytes isolated at P7 from CD36 knockout mice showed 30-40 % reduction in cardiomyocytes proliferation capacity at baseline and after 4F induction of proliferation compared to cardiomyocytes isolated from WT controls.

These findings suggest that CD36 is needed to prime the CMs to proliferate, and this can be, at least partially, through provision of energy requirements through β-oxidation of fatty acids.

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