# Got sugar? Skeletal muscle development responds to nutrient availability

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A new study finds that restricted nutrient availability prevents muscle stem cells from growing into mature muscle cells. The research, published by Cell Press in the May issue of the journal *Developmental Cell*, provides exciting new information about how developing muscle cells sense and respond to nutrient levels. The study adds a new twist to ongoing research into the effects of caloric restriction on physiology and aging and may lead to new therapeutic avenues for muscle wasting.

Although it is certainly rational to expect that access to nutrients, such as the simple sugar glucose, has a profound impact on the development of human cells, the cellular strategies for responding to fluctuations in nutrient availability are not well understood. Drs. Vittorio Sartorelli and Marcella Fulco from the National Institutes of Health investigated how the availability of glucose affects the ability of muscle stem cells, called myoblasts, to develop (or “differentiate”) into mature skeletal muscle fibers.

The researchers found that glucose restriction (GR) impaired differentiation of skeletal myoblasts and activated AMP-activated protein kinase (AMPK). These results define a pathway in which activation of AMPK in response to low glucose levels stimulates expression of the NAD+ biosynthetic enzyme Nampt. NAD+ is a known cofactor of SIRT1, which plays an important role in numerous physiological processes, including differentiation of skeletal muscle cells, and has been implicated in regulation of lifespan and aging. Importantly, inhibition of AMPK, Nampt or SIRT1 resulted in skeletal

muscle cells that were oblivious to a nutrient poor environment and were able to differentiate under conditions that otherwise would not be suitable.

These results demonstrate that a defined pathway actively controls muscle differentiation in response to low nutrients. “We speculate that, functioning as a cellular checkpoint, the AMPK-Nampt-SIRT1 pathway may be activated by reduced nutrient availability to prevent cells from undertaking energy demanding processes – such as cell differentiation – during calorie-unfavorable conditions. On the other hand, once nutrients become available, the pathway is inactivated to allow resumption of physiological development,” offers Dr. Sartorelli.

The study has important implications that extend beyond muscle development. This mechanism also operates in adult tissues and thus would be part of the response to a dietary regimen that restricts caloric intake. Further, the researchers found that glucose restriction or treatment of skeletal muscle cells with metformin, a drug used to treat type II diabetes, had similar outcomes and resulted in the activation of SIRT1. “It is therefore possible that the well-known benefits that diabetics derive from lowering the calorie intake in their diet may be attributable to activation of the AMPK-Nampt-SIRT1 axis” comments Dr. Sartorelli. It is also attractive to speculate that AMPK and SIRT1 may prove to be rational targets for counteracting the devastating effects of muscle wasting.

Source: Cell Press