AMPK: How can we amp it up to fight disease?

The high prevalence of obesity, insulin resistance, type 2 diabetes and cardiovascular disease has made it clear that we need a better understanding of how our bodies store and use energy when we overload them with excess food. There are a number of different molecules in each cell of our body that regulate the energy that we acquire from food. When energy supplies are high (e.g. immediately following a meal) and there is more than enough energy available to sustain our basal metabolism, a protein complex called mammalian target of rapamycin complex 1 (mTORC1) helps use this energy for growth or stores it for later use in molecules such as fatty acids. When energy supplies are low (e.g. during a fast) another complex, AMP-activated protein kinase (AMPK), helps mobilize that stored energy in several ways, one of which includes breaking down fatty acids. Activation of AMPK has also been associated with a reduction in inflammation and oxidative stress, harmful processes that are often observed in obesity, diabetes and other chronic diseases.

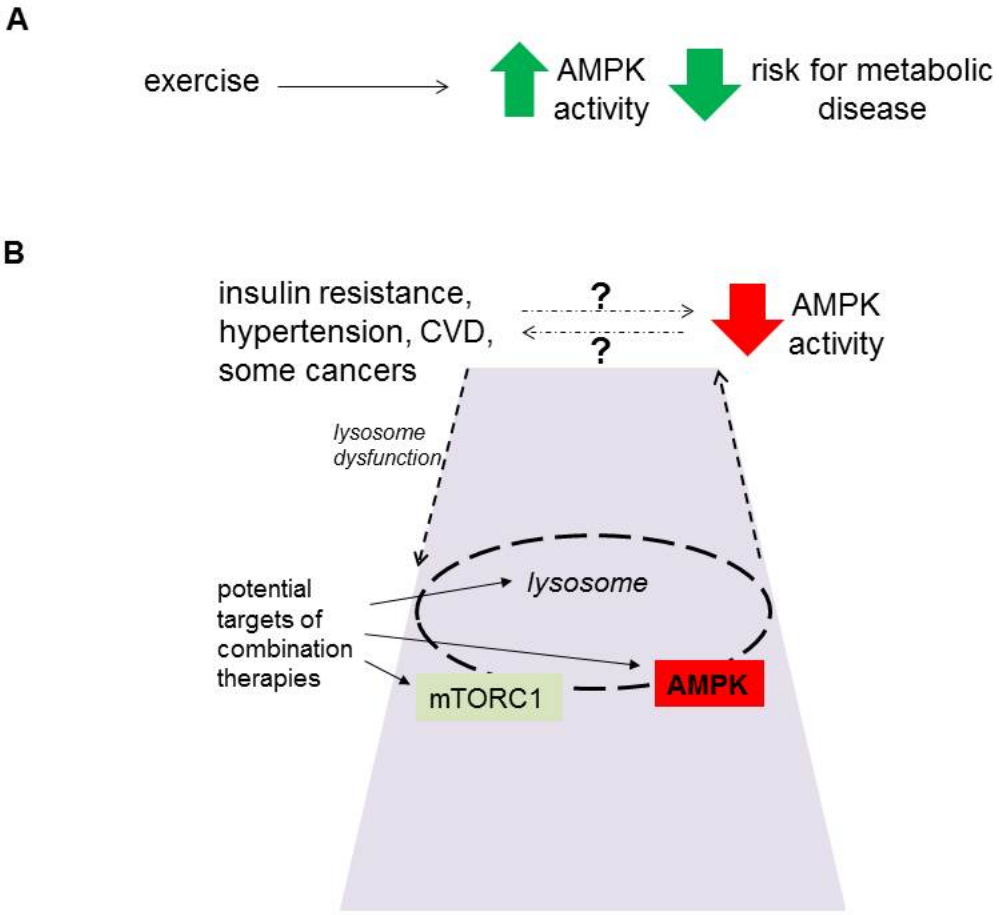

Fig. 1. AMPK links exercise and metabolic disease. Exercise has been shown to increase AMPK activity in several tissues, which can alter a number of processes to decrease risk for metabolic disease (A). Metabolic diseases have been associated with decreased AMPK activity (B). It is not

clear whether decreased AMPK activity is a cause or result of metabolic disease, but evaluation of disease-induced changes in the lysosome, a site of AMPK activation, may help clarify the role of AMPK. Lysosome dysfunction may impair AMPK activation or disrupt its relationship with mTORC1. Area shaded in purple indicates those relationships that are not well-established and require further inquiry, but that may lead to new AMPK-based combination therapies for metabolic diseases.

During metabolic disease, AMPK activity declines in muscle, liver, fat and blood vessels, perhaps due to exposure to high levels of sugar and fat (that are often observed in tissues of obese and diabetic patients). Recent work in cells in culture has suggested that the way in which a cell senses and responds sugar and fat may not only depend on AMPK, but also on mTORC1. Activation of both of these proteins involves a part of the cell called the lysosome, an organelle that is responsible for recycling old and damaged proteins and organelles. A better understanding of how overnutrition affects the lysosome might improve our understanding of how AMPK and mTORC1 are affected by obesity and diabetes. While some AMPK-activating drugs such as metformin and statins have metabolic benefits, they do not completely resolve the health problems associated with diabetes and obesity. This is likely partly due to the fact that AMPK interacts with a number of other components, and is only one contributing piece of the puzzle. Therefore, consideration of AMPK within the context of mTORC1 and lysosomal health may ultimately lead to the development of combination therapies for metabolic diseases such as diabetes and insulin resistance.

Perhaps more important than its potential role in disease treatment is AMPK's role in disease prevention. Studies in both animals and humans have shown that exercise is a potent activator of AMPK in the muscle, liver, heart, fat and pancreas. In muscle, AMPK is thought to be at least one of the factors contributing to the benefits of exercise perhaps by improving the uptake of sugar from the blood or the breakdown of fat. Interestingly, exercise-induced activation of AMPK is attenuated in patients with obesity or type 2 diabetes compared to healthy adults, suggesting not only that disease may impair AMPK function, but that obese patients may need to exercise more than healthy adults to achieve the same benefits of AMPK activation. This also suggests that we can maximize the AMPK-exercise benefits by using exercise as a preventative means to boost AMPK activity and perhaps delay the onset of disease.

In our current culture of overnutrition, where 1 in 4 American adults are prediabetic, exercise is an excellent side effect-free way to help mitigate metabolic disease and activate AMPK. Once metabolic disease sets in though, pharmaceuticals that solely target AMPK may not offer complete cures. Instead, AMPK-based combination therapies, perhaps involving mTORC1 and the lysosome may produce more effective treatments in the future.

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