**How eating feeds in to the circadian clock**

We live in a 24-hour world, where the time taken for the earth to rotate on its axis provides a continuous rhythm to our environment - the day-night cycle. This occupies a fundamental place in our biology; as a result of evolving under this daily cycle, animals, plants, fungi and some bacteria have developed timing mechanisms that tune their physiology and behaviour to a 24-hour beat. Circadian rhythms are thought to confer an adaptive advantage, as they allow organisms to anticipate daily changes in their environment. So, for example, animals can time when they forage for food to avoid the times of day when predators are active, and plants can ramp-up the machinery required for photosynthesis to anticipate sunrise and thereby maximise light-gathering efficiency.

For humans, and other mammals, this biological clock drives daily hormonal and temperature cycles, as well as variation in reaction time and wound healing capacity and, of course, the sleep-wake cycle. Importantly, these ‘circadian rhythms’ (from the Latin ‘circa’ – around and ‘dies’ – a day) persist in the absence of environmental cycles – which can be tested under controlled laboratory conditions. Critically, countless such experiments have revealed that daily oscillations in our biology are not merely a direct response to external change, but are intrinsically generated within every cell.

In order to accurately predict daily environmental variation, organisms need to be able to synchronize their internal, autonomously produced, circadian rhythms with the rhythm of the outside world. The best known synchronizing cue is the day-night cycle, where timing of light reaching the eyes in mammals is processed by the brain, which then signals to the rest of the body. Another major synchronizing signal in mammals is the time at which food is eaten. Unlike light/dark signals, the mechanism by which feeding synchronizes circadian rhythms was not well understood. It was clear, however, that time of feeding is an extremely important cue for circadian rhythms, and that eating at unusual times - as during shiftwork, when food is often consumed at night – is associated with a higher prevalence of a range of illnesses, including type 2 diabetes and some forms of cancer.

At the outset of our investigation, we noticed that both insulin and the related insulin-like growth factor-1 (commonly known as IGF-1) could shift the timing of circadian rhythms across a broad range of cultured cells and tissues. We pursued this to elucidate the mechanism by which insulin/IGF-1 shifts cellular rhythms, finding that in cultured cells and whole mice insulin/IGF-1 elicited a rapid increase in the activity of ‘PERIOD’ clock proteins. Based on pioneering experiments with fruit flies during the 1970’s, the activity of PERIOD proteins is now well established as being critical for determining the timing of the circadian oscillation in mammalian cells. By using drugs that inhibit major steps in the insulin signaling pathway, we found that increases in PERIOD occurred through the cellular messenger PIP3 to activate the downstream protein complex mTORC, an important regulator of protein production in cells. mTORC regulates many cellular functions however, and so we found that the selective increase in PERIOD was achieved by simultaneous degradation of micro interfering RNAs (miRNAs) that normally suppress the production of PERIOD proteins.

Blood levels of insulin and free IGF-1 rise in response to feeding, so we next asked whether insulin and IGF-1 might be the major signal synchronizing mammalian circadian rhythms with feeding. To answer this, we measured how quickly mice shift their circadian rhythms to synchronize with a 12h delay in their feeding time. Within 5 days, control mice shifted their circadian rhythms to match feeding time, whereas the mice receiving a drug in their drinking water that blocked insulin/IGF-1 signaling showed no significant shift over this time. This suggests that insulin/IGF-1 signaling is a major factor that communicates time of feeding to synchronise circadian rhythms in cells throughout the body.

Most people follow a consistent timing relationship between the major daily timing cues of light and feeding time. Broadly speaking, we eat food when it is daylight. Changing the timing relationship between these cues – in shift work, for example – is a risk factor for a number of chronic age-related diseases. It is our hope that identification of the molecular mechanisms – such as insulin signaling – by which external timing cues interact with our innate circadian rhythms to influence health outcomes will inform development of methods to alleviate the detrimental health effects of shift working and other forms of circadian disruption.