tolerate old parasites brought from the old one. The expensive immune defenses of *H. axyridis* have, thus, allowed *Nosema* to be used as a biological weapon against sympatric competitors, a trait only revealed as a pre-adaptation to invasiveness when the insect was introduced by human agency into new ecosystems far from home.

**References**


**CELL BIOLOGY**

**Insulin Finds Its Niche**

Seth W. Cheetham and Andrea H. Brand

Coordination of organ growth and metabolism in response to changing environmental conditions is essential for physiological homeostasis. A central metabolic control mechanism in multicellular organisms is insulin signaling. Under conditions of elevated blood sugar, insulin promotes the storage of glucose in tissues such as muscle, fat, and liver. Classically, the role of insulin signaling is systemic. In mammals, insulin is produced by pancreatic beta cells and released into the bloodstream in response to increased concentrations of blood glucose, inducing global changes in growth and metabolism. Intriguingly, recent studies have demonstrated that insulin signaling can also occur locally, over a short range. Why have local insulin signaling? Local signals allow organ-specific, rather than organismal responses to changing environmental conditions (see the figure). This allows the modulation of the growth and development of individual tissues to be separately controlled, and raises the question of whether this phenomenon could be exploited for therapeutic strategies. Many of these recent findings have arisen from research in invertebrates; however, there are striking parallels in mammals.

The dynamic control of stem cell populations in response to a variety of stimuli is critical to organismal adaptation to environmental conditions. Local insulin signaling has emerged as playing a critical role in regulating stem cell behavior. In the fruit fly *Drosophila melanogaster*, reactivation of neural stem cells from a period of quiescence is critically dependent on the availability of dietary protein (1). Amino acids are sensed by the fat body, the *Drosophila* equivalent of the mammalian liver and adipose tissue. In the presence of nutrients, the fat body signals to neuroendocrine cells in the brain to secrete insulin-like peptides (dILPs). Circulating dILPs reach target cells in various organs and tissues where they bind to the insulin receptor and activate the conserved phosphatidylinositol 3-kinase (PI3-kinase)–Akt signaling cascade, triggering cell growth and proliferation (2). It was initially speculated that this systemic insulin signaling was responsible for neural stem cell reactivation (3). Surprisingly, however, neural stem cells respond only to locally produced insulin provided by neighboring glial cells that comprise a stem cell niche. The glia secrete the insulin-like peptide dILP6, which stimulates neural stem cells to exit from quiescence. Blocking this insulin release impairs stem cell reactivation. Conversely, forced expression of dILP6 in glial cells rescues neural stem cell reactivation under starvation conditions (4, 5). Thus, the stem cell niche acts as a buffer that lates stem cells from systemic signals and restricts their response to local signals.

Interestingly, local insulin signaling is not a unique feature of the nervous system but is also found in the intestine. Upon feeding, *Drosophila* intestinal stem cells proliferate extensively within their niches. This increase in the stem cell population is induced by dILP3, which is secreted in a nutrient-dependent manner by the visceral muscle that underlies intestinal stem cells. Depletion of dILP3 in this muscle greatly reduces feeding-dependent proliferation (6). The distinct roles for dILP3 and dILP6 and their differential expression patterns suggest that other dILPs may also have defined roles in specific tissues (7).

The modulation of stem cell function by insulin signaling appears to be an evolutionarily conserved mechanism. Mammalian pluripotent stem cells rely on local signals from support cells to maintain self-renewal...
and identity. Evidence from in vitro studies demonstrated that human embryonic stem cells depend on basic fibroblast growth factor (bFGF) signaling. bFGF stimulates fibroblast-like support cells to produce insulin-like growth factor-2 (IGF-2), a factor sufficient to maintain human embryonic stem cell cultures (7). Similarly, neonatal spermatogonial stem cell pluripotency is maintained by the secretion of IGF-1 by Leydig support cells in vitro (8). In the mouse small intestine, IGF-1 is expressed in the subepithelial muscle cells (9), suggesting that mammalian intestinal growth may be regulated by a mechanism similar to that observed in Drosophila. Vertebrate niche cells can relay a variety of stimuli through the insulin signaling cascade. Cone photoreceptor cells in the teleost retina produce IGF-1 in a time-of-day–dependent cycle. Application of IGF-1 increases the proliferation of rod progenitor cells in vivo, with the greatest sensitivity at night, coinciding with peak endogenous IGF-1 expression. Conversely, blocking the IGF-1 receptor, which is expressed on the rod progenitor cells, decreases their proliferation (10). Thus, localized insulin signaling can be controlled by nonmetabolic stimuli and may contribute to progenitor cell response to diverse external stimuli.

Local insulin also plays a role in mediating the proliferation of progenitor cells in response to tissue damage. In rats, induction of focal ischemia causes neuronal cell death. After ischemia, brain astrocytes (a type of glial cell) near the damaged area produce IGF-1, promoting proliferation of neighboring neural progenitors in the dentate gyrus of the adult rat hippocampus (11). Forced expression of IGF-1 in astrocytes promotes localized overgrowth of the brain in rodents (11), whereas direct infusion of IGF-1 into specific brain regions can induce neurogenesis in healthy adult mammalian brains (12). This parallels the role of glial-derived insulin in increasing neural stem cell proliferation in Drosophila (4, 5). Other stimuli, including exercise, also promote neurogenesis in the proliferative subventricular zone and dentate gyrus regions of the adult mouse brain, although this appears to be through systemic IGF-1 signaling (13, 14).

The discovery that stem cells are sensitive to locally produced insulin could open new avenues in the use of IGFS to activate particular stem cell populations after tissue damage or disease. The cerebrospinal fluid provides access for cerebral cortical progenitor cells in the mouse brain to insulin-like peptides (15). Infusion of insulin-like peptides into this fluid or into particular brain regions may allow moderation of the effects of injury or neurodegeneration.

Differences in local versus systemic signaling under caloric restriction may favor the maintenance rather than proliferation of stem cell pools. This may help to explain the apparent contradiction that, although reduced insulin signaling increases life span in mammals and invertebrates, insulin signaling has a neuroprotective effect in the central nervous system (16).

Several key questions are yet to be answered about local insulin signaling, including how systemic signals are functionally coupled to niche insulin signals, how different niche signals integrate to control stem cell behavior, and how local insulin signaling changes in aging and disease. Understanding these interactions will enable a greater understanding of stem cell dynamics in response to external signals and metabolic state.

MATERIALS SCIENCE

Quartz on Silicon

C. Jeffrey Brinker and Paul G. Clem

The integration of quartz with silicon may provide a route to fabricate advanced piezoelectric devices.

The on-chip integration of piezoelectric quartz would be highly beneficial for chemical sensing and accurate timing circuits. However, to date, it has not been possible to achieve single-orientation, single-variant silicon dioxide films with high piezoelectric activity. On page 827 of this issue, Carretero-Genevrier et al. (1) demonstrate the formation of oriented piezoelectrically active α-quartz thin films directly on silicon. Although the growth mechanism and piezoelectric properties require fuller development, their approach may be an attractive route for developing integrated piezoelectric devices.

Quartz, one of 11 crystalline polymorphs of silicon dioxide, SiO$_2$, is the second most abundant mineral on Earth (2). Most forms of SiO$_2$ are composed of SiO$_2$ tetrahedra linked together by bridging oxygens to form a rigid three-dimensional network. The relative flexibility of the bond angles accommodates different crystalline symmetries and enhances the ability of SiO$_2$ to form amorphous silica glass. The low-temperature form of quartz, α-quartz, possesses trigonal symmetry, a bond angle of 144°, and density of 2.65 g/cm$^3$. Due to its high hardiness, natural quartz is used as an abrasive (2). Quartz’s most important technological use derives from its piezoelectric behavior (3), which is indispensable in electronics for timing control in clocks and microprocessors (4).

The piezoelectric effect, the conversion of strain into electricity (5), requires inversion asymmetry of the crystalline lattice, which is satisfied by the trigonal symmetry of α-quartz; β-quartz, which is stable above 573°C, and β-cristobalite, which is the typical devitrification (crystallization) product of amorphous silica, have hexagonal and tetrahedral symmetry, respectively, and are not piezoelectric. Although abundant, natural quartz seldom has the purity and quality needed for device applications, and almost all quartz oscillators are prepared by “slicing” bulk synthetic quartz crystals prepared hydrothermally (see the figure, panel A). Carretero-Genevrier et al. form α-quartz thin films directly on silicon by devitrification of amorphous Sr- or Ba-doped mesoporous

References

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