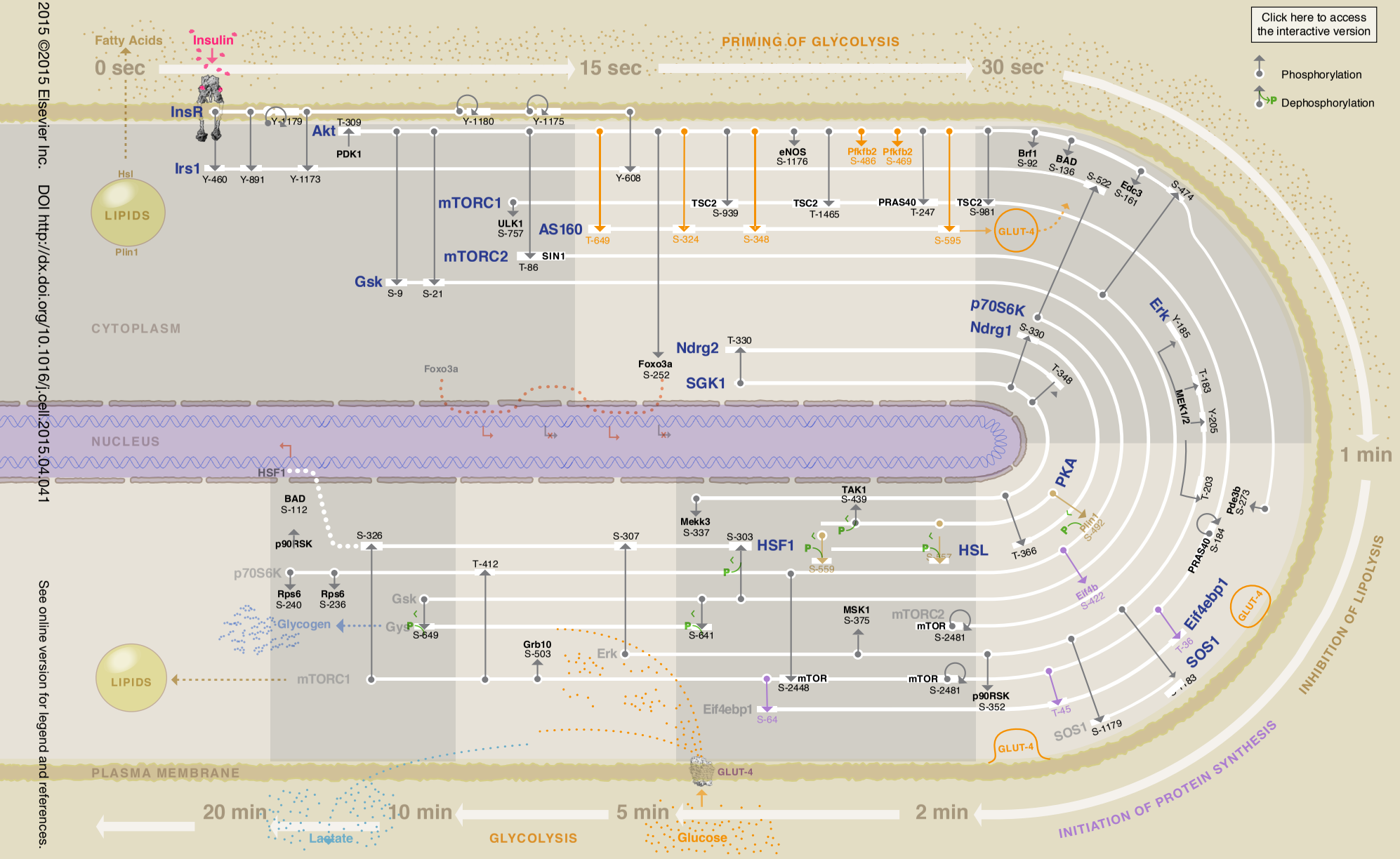
ENHANCED SnapShot: Insulin/IGF1 Signaling

David K.G. Ma,[1,2] Christian Stolte,[3] James R. Krycer,[4] David E. James,[4,5] and Seán I. O'Donoghue[1,3]
[1]Garvan Institute of Medical Research, Darlinghurst NSW 2010, Australia, [2]School of Computer Science and Engineering, UNSW Sydney, NSW 2052, Australia, [3]CSIRO, North Ryde NSW 1670, Australia, [4]Charles Perkins Centre, School of Molecular Bioscience, The University of Sydney, NSW 2006, Australia, [5]Sydney Medical School, The University of Sydney, NSW 2006, Australia

Cell



ENHANCED SnapShot: Insulin/IGF1 Signaling

David K.G. Ma,[1,2] Christian Stolte,[3] James R. Krycer,[4] David E. James,[4,5] and Seán I. O'Donoghue[1,3]
[1]Garvan Institute of Medical Research, Darlinghurst NSW 2010, Australia
[2]School of Computer Science and Engineering, UNSW Sydney, NSW 2052, Australia
[3]CSIRO, North Ryde NSW 1670, Australia
[4]Charles Perkins Centre, School of Molecular Bioscience, The University of Sydney, NSW 2006, Australia
[5]Sydney Medical School, The University of Sydney, NSW 2006, Australia

The insulin/IGF1 signaling pathway (ISP) plays an essential role in long-term health. Some perturbations in this pathway are associated with diseases such as type 2 diabetes (George et al., 2004); other perturbations extend lifespan in worms, flies, and mice (Ziv and Hu, 2011). The ISP regulates many biological processes, including energy storage, apoptosis, transcription, and cellular homeostasis. Such regulation involves precise rewiring of temporal events in protein phosphorylation networks; these events can now be observed in detail using high-throughput mass spectrometry (Humphrey et al., 2013).

To address the challenge of displaying the resulting multi-dimensional data sets, we developed Minardo, a novel strategy for visualizing time-course events in cellular systems (Ma et al., 2013). Beginning with the moment that the adipocyte perceives an increase in extracellular insulin (upper-left), the Minardo layout shows the progressive triggering of nodes in the first 20 min of the ISP cascade, with time flowing in a clockwise direction. Gray arrows indicate phosphorylation or dephosphorylation events, from kinase (arrow stem) to substrate (arrowhead), with position indicating the time of half-maximal change in phosphorylation state. Some proteins (or complexes) play major roles in ISP and hence have events at multiple times; these are represented as white tracks. Residue numbering refers to mouse proteins, as used by Humphrey et al. (2013).

We see that the insulin signal is rapidly transduced via the insulin receptor and the scaffold protein IRS-1 to the serine/threonine kinase Akt, which then targets substrates involved in numerous biological pathways (many involving 14-3-3). One prominent example is glucose disposal: Akt phosphorylates AS160 to promote glucose uptake, via provocation of the translocation of intracellular GLUT4 glucose transporter vesicles to the plasma membrane of the cell (Stöckli et al., 2011), and phosphorylates PFKFB2 to stimulate glycolysis (Deprez et al., 1997). The kinase GSK3α/β is inhibited by Akt, which in turn derepresses glycogen synthase to facilitate incorporation of the incoming glucose into glycogen. In contrast, Akt phosphorylates PRAS40 and TSC2 to activate mTORC1, a key kinase that drives lipid and amino acid metabolism (Efeyan et al., 2012). Thus, Akt straddles several kinase cascades, evident from the progression of the tracks in the Minardo layout.

Beyond Akt, insulin represses protein kinase A (PKA) by activating Pde3b to hydrolyze cAMP, an allosteric activator of PKA (Kitamura et al., 1999; Onuma et al., 2002). This deactivates downstream substrates such as Hsl and Plin1, leading to reduced lipid breakdown and free fatty-acid release within about 1 min. Thus, insulin signaling acts through several kinases and a multitude of substrates to promote energy storage and prevent energy mobilization (Saltiel and Kahn, 2001).

Cellular metabolism is regulated alongside gene expression, with mTORC1 playing a central role. mTORC1 and its downstream kinase, p70S6K, phosphorylate a range of proteins involved in translation (Rps6, Eif4b, Ei4ebp1) while promoting the heat-shock response protein Hsf1. Insulin signaling also promotes mRNA stability by phosphorylation of Brf1 and Edc3, together stimulating a global increase in protein synthesis. mTORC1 also instructs the cell that nutrients are not limiting by phosphorylating ULK1, which curbs autophagy (Efeyan et al., 2012). Furthermore, insulin signaling prevents apoptosis by inhibiting Bad from binding Bcl and trapping the transcription factor Foxo3a within the cytoplasm. This coordinated regulation ensures that the enormous energetic demands of these various biosynthetic processes are balanced by fuel supply, particularly from glucose metabolism.

This complex network is maintained by crosstalk between key kinases, shown by connections between the corresponding tracks in the Minardo layout. For instance, after Akt is phosphorylated at T308, it phosphorylates SIN1, which activates mTORC2 to phosphorylate Akt at S473, completely activating Akt (Humphrey et al., 2013). In contrast, mTORC1 phosphorylates Grb10, and p70S6K phosphorylates IRS1 and mTOR, together attenuating insulin signaling. Such feedback mechanisms fine-tune the appropriate responses to environmental changes.

In summary, insulin/IGF1 signaling involves several key kinase nodes that target many substrates, thus intertwining metabolism with numerous other biological processes.

For an animated version of this SnapShot, please see http://www.cell.com/cell/enhanced/odonoghue.

REFERENCES

Deprez, J., Vertommen, D., Alessi, D.R., Hue, L., and Rider, M.H. (1997). J. Biol. Chem. 272, 17269–17275.

Efeyan, A., Zoncu, R., and Sabatini, D.M. (2012). Trends Mol. Med. 18, 524–533.

George, S., Rochford, J.J., Wolfrum, C., Gray, S.L., Schinner, S., Wilson, J.C., Soos, M.A., Murgatroyd, P.R., Williams, R.M., Acerini, C.L., et al. (2004). Science 304, 1325–1328.

Humphrey, S.J., Yang, G., Yang, P., Fazakerley, D.J., Stöckli, J., Yang, J.Y., and James, D.E. (2013). Cell Metab. 17, 1009–1020.

Kitamura, T., Kitamura, Y., Kuroda, S., Hino, Y., Ando, M., Kotani, K., Konishi, H., Matsuzaki, H., Kikkawa, U., Ogawa, W., and Kasuga, M. (1999). Mol. Cell. Biol. 19, 6286–6296.

Ma, D.K.G., Stolte, C., Kaur, S., Bain, M., and O'Donoghue, S.I. (2013). AIP Conf. Proc. 1559, 185–196.

Onuma, H., Osawa, H., Yamada, K., Ogura, T., Tanabe, F., Granner, D.K., and Makino, H. (2002). Diabetes 51, 3362–3367.

Saltiel, A.R., and Kahn, C.R. (2001). Nature 414, 799–806.

Stöckli, J., Fazakerley, D.J., and James, D.E. (2011). J. Cell Sci. 124, 4147–4159.

Ziv, E., and Hu, D. (2011). Ageing Res. Rev. 10, 201–204.

  DOI http://dx.doi.org/10.1016/j.cell.2015.04.041