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Scientific News
3rd of November 2013
Sven Bulterijs



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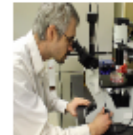


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Why plants usually live longer than animals

24 October 2013



Stem cells are crucial for the continuous generation of new cells. Although the importance of stem cells in fuelling plant growth and development still many questions on their tight molecular control remain unanswered. Plant researchers at VIB and [Ghent University](#) discovered a new step in the complex regulation of stem cells. Today, their results are published online in this week's issue of Science Express.

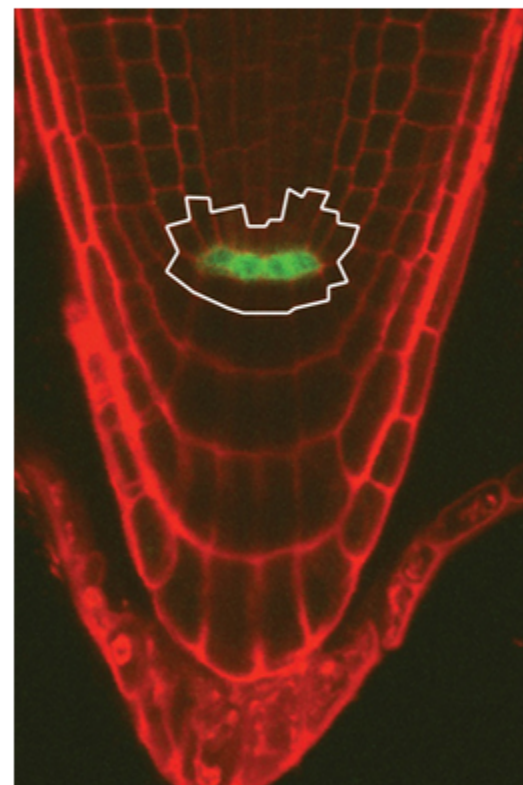
Lieven De Veylder: "Our data suggest that certain organizing stem cells in plant roots are less sensitive for DNA-damage. Those cells hold an original and intact DNA copy which can be used to replace damaged cells if necessary. Animals rely on a similar mechanism but most likely plants have employed this in a more optimized manner. This could explain why many plants can live for more than hundreds of years, while this is quite exceptional for animals."

Quiescent organisers of plant growth

Plant growth and development depend on the continuous generation of new cells. A small group of specialized cells present in the growth axes of a plant is driving this. These so-called stem cells divide at a high frequency and have the unique characteristic that the original mother cell keeps the stem cell activity while the daughter cell acquires a certain specialization. Besides these stem cells, plant roots also harbor organizing cells. These organizing cells divide with a three- to ten-fold lower frequency, therefore often referred to as quiescent center cells. The organizing cells control the action of the surrounding stem cells and can replace them if necessary.

A new molecular network

For almost 20 years, scientists all over the world have been studying the action of the stem cells and that of their controlling organizing cells. Until now it was not known how quiescent and actively dividing cells could co-exist so closely and which mechanisms are at the basis of the quiescent character. Plant researchers at VIB and Ghent University have now identified a new molecular network that increases our understanding of stem cell regulation and activity. Central in this process is the discovery of a new protein, the **ERE115 transcription factor**. The scientists demonstrated that the



A root tip of the model plant Arabidopsis thaliana. The organizing cells are visualized by the green fluorescence and are surrounded by the stem cells (within the white frame).

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ARTICLE

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Reprogramming *in vivo* produces teratomas and iPS cells with totipotency features

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Reprogramming of adult cells to generate induced pluripotent stem cells (iPS cells) has opened new therapeutic opportunities; however, little is known about the possibility of *in vivo* reprogramming within tissues. Here we show that transitory induction of the four factors *Oct4*, *Sox2*, *Klf4* and *c-Myc* in mice results in teratomas emerging from multiple organs, implying that full reprogramming can occur *in vivo*. Analyses of the stomach, intestine, pancreas and kidney reveal groups of dedifferentiated cells that express the pluripotency marker NANOG, indicative of *in situ* reprogramming. By bone marrow transplantation, we demonstrate that haematopoietic cells can also be reprogrammed *in vivo*. Notably, reprogrammable mice present circulating iPS cells in the blood and, at the transcriptome level, these *in vivo* generated iPS cells are closer to embryonic stem cells (ES cells) than standard *in vitro* generated iPS cells. Moreover, *in vivo* iPS cells efficiently contribute to the trophectoderm lineage, suggesting that they achieve a more plastic or primitive state than ES cells. Finally, intraperitoneal injection of *in vivo* iPS cells generates embryo-like structures that express embryonic and extraembryonic markers. We conclude that reprogramming *in vivo* is feasible and confers totipotency features absent in standard iPS or ES cells. These discoveries could be relevant for future applications of reprogramming in regenerative medicine.

PROTEOMICS

Commentary

Oncogene-induced cellular senescence elicits an anti-Warburg effect

Rosamonde E. Banks*

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Keywords:

Histones; Oncogene-induced senescence; Pyruvate dehydrogenase; Systems biology; Warburg effect







Oncogene-induced senescence is now recognized as being an important mechanism in protecting against cancer. The phenotypic consequences, i.e., the inhibition of cell proliferation, are well described in model systems and specific events/key players defined. However, there is still the need to understand, at a more global level, the network of events involved both in terms of cause and consequence. This paper shows the power of systematic proteomic analyses, both targeted and global, in addressing such biological questions, highlighting the widespread nature of histone acetylation changes, and the opposite metabolic changes to those seen in the Warburg effect.

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Hierarchical Mechanisms for Direct Reprogramming of Fibroblasts to Neurons

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SUMMARY

Direct lineage reprogramming is a promising approach for human disease modeling and regenerative medicine, with poorly understood mechanisms. Here, we reveal a hierarchical mechanism in the direct conversion of fibroblasts into induced neuronal (iN) cells mediated by the transcription factors *Ascl1*, *Brn2*, and *Myt1l*. *Ascl1* acts as an “on-target” pioneer factor by immediately occupying most cognate genomic sites in fibroblasts. In contrast, *Brn2* and *Myt1l* do not access fibroblast chromatin productively on their own; instead, *Ascl1* recruits *Brn2* to *Ascl1* sites genome wide. A unique trivalent chromatin signature in the host cells predicts the permissiveness for *Ascl1* pioneering activity among different cell types. Finally, we identified *Zfp238* as a key *Ascl1* target gene that can partially substitute for *Ascl1* during iN cell reprogramming. Thus, a precise match between pioneer factors and the chromatin context at key target genes is determinative for transdifferentiation to neurons and likely other cell types.

Muscle Mitohormesis Promotes Longevity via Systemic Repression of Insulin Signaling

SUMMARY

Mitochondrial dysfunction is usually associated with aging. To systematically characterize the compensatory stress signaling cascades triggered in response to muscle mitochondrial perturbation, we analyzed a *Drosophila* model of muscle mitochondrial injury. We find that mild muscle mitochondrial distress preserves mitochondrial function, impedes the age-dependent deterioration of muscle function and architecture, and prolongs lifespan. Strikingly, this effect is mediated by at least two pro-longevity compensatory signaling modules: one involving a muscle-restricted redox-dependent induction of genes that regulate the mitochondrial unfolded protein response (UPR^{mt}) and another involving the transcriptional induction of the *Drosophila* ortholog of insulin-like growth factor-binding protein 7, which systemically antagonizes insulin signaling and facilitates mitophagy. Given that several secreted IGF-binding proteins (IGFBPs) exist in mammals, our work raises the possibility that muscle mitochondrial injury in humans may similarly result in the secretion of IGFBPs, with important ramifications for diseases associated with aberrant insulin signaling.

Sperm competition drives the evolution of suicidal reproduction in mammals

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Edited by James H. Brown, University of New Mexico, Albuquerque, NM, and approved August 29, 2013 (received for review June 5, 2013)

Suicidal reproduction (semelparity) has evolved in only four genera of mammals. In these insectivorous marsupials, all males die after mating, when failure of the corticosteroid feedback mechanism elevates stress hormone levels during the mating season and causes lethal immune system collapse (die-off). We quantitatively test and resolve the evolutionary causes of this surprising and extreme life history strategy. We show that as marsupial predators in Australia, South America, and Papua New Guinea diversified into higher latitudes, seasonal predictability in abundance of their arthropod prey increased in multiple habitats. More-predictable prey peaks were associated with shorter annual breeding seasons, consistent with the suggestion that females accrue fitness benefits by timing peak energy demands of reproduction to coincide with maximum food abundance. We demonstrate that short mating seasons intensified reproductive competition between males, increasing male energy investment in copulations and reducing male postmating survival. However, predictability of annual prey cycles alone does not explain suicidal reproduction, because unlike insect abundance, peak ovulation dates in semelparous species are often synchronized to the day among years, triggered by a species-specific rate of change of photoperiod. Among species with low postmating male survival, we show that those with suicidal reproduction have shorter mating seasons and larger testes relative to body size. This indicates that lethal effort is adaptive in males because females escalate sperm competition by further shortening and synchronizing the annual mating period and mating promiscuously. We conclude that precopulatory sexual selection by females favored the evolution of suicidal reproduction in mammals.

evolve lethal male competition have been proposed: (i) females are constrained to leave a 12-mo gap between litters because a peak in arthropod prey occurs annually in their seasonally predictable forest habitats, weaning success depends on this spike in food, and females have a long lactation time relative to body size (a marsupial trait). Environmental causes of mortality (rife in small mammals) mean that adult males of these species seldom survive for a year after maturity, and lethal competition in the first season is adaptive because males are unlikely to breed again (Braithwaite and Lee's hypothesis) (2); (ii) phylogenetic predisposition (an unknown developmental constraint locking modern taxa into nonadaptive male die-off) (7); (iii) accumulation of deleterious mutations after breeding (6); (iv) poor survival of breeding females resulting in male bet-hedging (spreading the risk of offspring death among many mates) and therefore extreme male promiscuity (8); or (v) altruism (males sacrificing themselves to avoid competing with the next generation for limited food) (2, 3, 9). Braithwaite and Lee's adaptive framework, based on the exceptional lactation time of dasyurids, is the only one of these suggestions to address why die-off has not evolved more widely in small mammals. This hypothesis was based on the traits of a small number of forest-dwelling species (2) and has been criticized because prey cycles appear to be less synchronized between years than the reproductive cycles of semelparous mammals (9). However, habitat and latitudinal effects on seasonality of insect abundance have not been quantified at continental scales, and dasyurid species with die-off occur in diverse, nonforest habitats (7, 10).

Alternative explanations have proposed that peculiarities of the mating system lead to extreme sexual selection and that this

Higher levels of advanced glycation endproducts in human carotid atherosclerotic plaques are associated with a rupture-prone phenotype

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Aims

Rupture-prone atherosclerotic plaques are characterized by inflammation and a large necrotic core. Inflammation is linked to high metabolic activity. Advanced glycation endproducts (AGEs) and their major precursor methylglyoxal are formed during high metabolic activity and can have detrimental effects on cellular function and may induce cell death. Therefore, we investigated whether plaque AGEs are increased in human carotid rupture-prone plaques and are associated with plaque inflammation and necrotic core formation.

Methods and results

The protein-bound major methylglyoxal-derived AGE 5-hydro-5-methylimidazolone (MG-H1) and N^ε-(carboxymethyl)lysine (CML) were measured in human carotid endarterectomy specimens ($n = 75$) with tandem mass spectrometry. MG-H1 and CML levels were associated with rupture-prone plaques, increased protein levels of the inflammatory mediators IL-8 and MCP-1 and with higher MMP-9 activity. Immunohistochemistry showed that AGEs accumulated predominantly in macrophages surrounding the necrotic core and co-localized with cleaved caspase-3. Intra-plaque comparison revealed that glyoxalase-1 (GLO-1), the major methylglyoxal-detoxifying enzyme, mRNA was decreased (-13% , $P < 0.05$) in ruptured compared with stable plaque segments. In line, in U937 monocytes, we found reduced (GLO-1) activity (-38% , $P < 0.05$) and increased MGO (346% , $P < 0.05$) production after stimulation with the inflammatory mediator TNF. Direct incubation with methylglyoxal increased apoptosis up to two-fold.

Conclusion

This is the first study showing that AGEs are associated with human rupture-prone plaques. Furthermore, this study suggests a cascade linking inflammation, reduced GLO-1, methylglyoxal- and AGE-accumulation, and subsequent apoptosis. Thereby, AGEs may act as mediators of the progression of stable to rupture-prone plaques, opening a window towards novel treatments and biomarkers to treat cardiovascular diseases.

REVIEWS

Energy metabolism and fertility—a balance preserved for female health

Sara Della Torre, Valeria Benedusi, Roberta Fontana and Adriana Maggi

Abstract | In female animals, energy metabolism and fertility are tightly connected, and reciprocally regulated. However, the relative contributions of metabolic and reproductive pathways have changed over the course of evolution. In oviparous animals, metabolic factors take precedence over fertility, enabling egg production to be inhibited in a nutritionally poor environment. By contrast, in placental mammals, the opposite occurs: the need to feed a developing embryo and neonate forces metabolic pathways to adapt to these reproductive needs. This physiological necessity explains why in female mammals alterations of gonadal activity, including age-dependent cessation of ovarian functions, are associated with a disruption of metabolic homeostasis and consequent inflammatory reactions that trigger the onset of metabolic, cardiovascular, skeletal and neural pathologies. This Review discusses how metabolic homeostasis and reproductive functions interact to optimize female fertility and explains the pathogenic mechanisms underlying the disordered energy metabolism associated with human ovarian dysfunction owing to menopause, polycystic ovary syndrome and Turner syndrome. Finally, this article highlights how hormone replacement therapy might aid the restoration of metabolic homeostasis in women with ovarian dysfunction.

Della Torre, S. et al. *Nat. Rev. Endocrinol.* advance online publication 22 October 2013; doi:10.1038/nrendo.2013.203

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With human life spans continuing to increase worldwide, the ability to keep brain functions intact into old age becomes ever more important. As the articles in this Clinical Collection illustrate, approaches to preventing or arresting neurodegeneration can take many forms, from lifestyle changes aimed at preserving the integrity of the brain, to pharmacological treatments and immunological interventions targeted at specific neurodegenerative disease mechanisms.

Produced with support of a grant from [Teva Pharmaceuticals](#)

Age-dependent dysregulation of innate immunity

Albert C. Shaw¹, Daniel R. Goldstein^{2,3} and Ruth R. Montgomery⁴

Abstract | As we age, the innate immune system becomes dysregulated and is characterized by persistent inflammatory responses that involve multiple immune and non-immune cell types and that vary depending on the cell activation state and tissue context. This ageing-associated basal inflammation, particularly in humans, is thought to be induced by several factors, including the reactivation of latent viral infections and the release of endogenous damage-associated ligands of pattern recognition receptors (PRRs). Innate immune cell functions that are required to respond to pathogens or vaccines, such as cell migration and PRR signalling, are also impaired in aged individuals. This immune dysregulation may affect conditions associated with chronic inflammation, such as atherosclerosis and Alzheimer's disease.

Liver support strategies: cutting-edge technologies

Benjamin Struecker, Nathanael Raschzok and Igor M. Sauer

Abstract | The treatment of end-stage liver disease and acute liver failure remains a clinically relevant issue. Although orthotopic liver transplantation is a well-established procedure, whole-organ transplantation is invasive and increasingly limited by the unavailability of suitable donor organs. Artificial and bioartificial liver support systems have been developed to provide an alternative to whole organ transplantation, but despite three decades of scientific efforts, the results are still not convincing with respect to clinical outcome. In this Review, conceptual limitations of clinically available liver support therapy systems are discussed. Furthermore, alternative concepts, such as hepatocyte transplantation, and cutting-edge developments in the field of liver support strategies, including the repopulation of decellularized organs and the biofabrication of entirely new organs by printing techniques or induced organogenesis are analysed with respect to clinical relevance. Whereas hepatocyte transplantation shows promising clinical results, at least for the temporary treatment of inborn metabolic diseases, so far data regarding implantation of engineered hepatic tissue have only emerged from preclinical experiments. However, the evolving techniques presented here raise hope for bioengineered liver support therapies in the future.

Struecker, B. et al. *Nat. Rev. Gastroenterol. Hepatol.* advance online publication 29 October 2013; [doi:10.1038/nrgastro.2013.204](https://doi.org/10.1038/nrgastro.2013.204)