**Supplementary Table S1:**

**Amount of "Pubmed"-results with the 7 best-regulated genes (July 2017)**

| Gene | "Cell cycle" AND "gene" |
|---|---|
| POLA1 | 10 |
| RHOB | 120 |
| TOP2A | 86 |
| TYMS | 31 |
| ANLN | 10 |
| SESN2 | 24 |
| DDIT4 | 46 |
| CCNA2 | 570 |
| CCNB1 | 3446 |

**Supplementary Table 2:**
**Anti-oxidant versus Pro-oxidant reports on regulators of mevalonate metabolism**

| A | Statins | |
|---|---|---|
| | **Statins Antiox** | **Statins Pro Ox = Pro ROS** |
| 1 | Normal podocytes PMID: 25240415 | A549 lung cancer cells (Sim upregulates SOD2) PMID: 25158572 |
| 2 | Cardiovasc system PMID: 25218292 | Mouse (feeding experiment) PMID: 25106875 |
| 3 | Renal and alveolar epithelial cells PMID: 25207459 | Malignant mesothelioma and lung cancer cells PMID: 25096993 |
| 4 | Cardiovasc system PMID: 25132378 | Rat hepatocytes PMID: 24754008 |
| 5 | Human B lymphoma cell PMID: 24518247 | In Melanoma by activating P53/P21 pathways PMID: 23933099 |
| 6 | Serum (human) PMID: 24401239 | Rat hepatocytes PMID: 23761184 |
| 7 | Human endothelial cells PMID: 24375611 | OCM-1 (choroidal melanoma) cells (PMID: 23727160 |
| 8 | Serum (human) PMID: 24263084 | A549 Lung cancer cells PMID: 23661227 |
| 9 | Skin (human) PMID: 24155025 | Human lymphoma cells PMID: 23449454 |
| 10 | Immune system (human) PMID: 24121054 | Myeloma PMID: 21958871 |
| 11 | Platelets (human) PMID: 23992095 | Lung cancer PMID: 23045963 |
| 12 | Cardiovasc system PMID: 23948511 | MCF-7 breast cancer PMID: 18608208 |
| 13 | Brain endothel (nucleus tractus solitarii) PMID: 23889671 | malignant pheochromocytomas and paragangliomasPMID: 24846270 |
| 14 | Cardiovasc system PMID: 23643589 | Human monocytes and macrophages PMID: 23159926 |
| 15 | Cardiovasc system PMID: 23608227 | Microvessels (swine) PMID: 18179927 |
| 16 | Human endothelial cells PMID: 23608189 | Myocardial tissue (swine) PMID: 18598320 |
| 17 | Mouse: high fat diet induced stress PMID: 23567805 | Human peripheral blood leukocytes PMID: 18161561 |
| 18 | Smooth muscle PMID: 23541442 | Human peripheral blood leukocytes PMID: 18485436 |
| 19 | BrainPMID: 23500607 | Atorvastatin (ATO) exposure (100μM) for 24h increased ROS levels, reduced the percentage of live myeloblast cells PMID: 25769432 |
| 20 | Human endothelial cells PMID: 23426387 | link between statin-induced mitochondrial oxidative stress and activation of the mitochondrial apoptosis signaling pathway in glycolytic skeletal muscle, PMID: 26414931 |
| 21 | Mouse endothelial cells PMID: 23259560 | Myopathy, characterized by mitochondrial oxidative stress, occurs in |

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| | | approximately 10 % of statin-treated patients. PMID: 27245589 |
| 22 | Human macrophages PMID: 23141585 | Statin increased hepatic reactive oxygen species (ROS) PMID: 27428373 |
| 23 | Human endothelial cells PMID: 23030449 | Statin-induced myotoxicity by ROS PMID: 28223230 |
| 24 | Human platelets PMID: 23022230 | atorvastatin (AS) can increase intracellular reactive oxygen species (ROS) and induce necrotic cell death autophagy in NIT-1 cells. PMID: 28004006 |
| 25 | Cardiovasc system PMID: 23016719 [ | Mitochondrial oxidative stress caused by statin treatment also signals for cellular antioxidant system responses such as catalase upregulation. These results suggest that the detrimental effects of statins on muscle mitochondria could be prevented by co-administration of a safe antioxidant such as creatine or CoQ10. PMID: 28424622 |
| 26 | Retinal pigment epithelium (RPE) PMID: 22918643 | Atorvastatin enhanced the cell killing effect of irradiation by reducing endogenous ROS levels and prolonging the lifespan of radiation-induced ROS via a decrease in the level of NOXs and SOD activity. PMID: 28260074 |
| 27 | Cardiovasc system PMID: 22862793 | Administration of simvastatin was followed by a decrease in activities of superoxide dismutase and cytochrome oxidase in rat mitochondria, which attested to dysfunction of the respiratory chain. PMID: 28239789 |
| 28 | Injured lung tissue PMID: 22701728 | |
| 29 | Muscle (rabbit) PMID: 22661508 | |
| 30 | Cardiovasc system PMID: 22652672 | |
| 31 | Cardiovasc system PMID: 22405985 | |
| 32 | Cardiovasc system PMID: 22394340 | |
| 33 | Human Kidney PMID: 22386936 | |
| 34 | Cochlear tissue (mouse ear) PMID: 22366511 | |
| 35 | Cardiomyocytes PMID: 22365145 | |
| 36 | Cardiovasc system PMID: 22293859 | |
| 37 | Diabetic Polyneuropathy PMID: 25214797 | |
| 38 | Arsenic-induced hypertension PMID: 25218292 | |
| 39 | Reduction of the proadhesive and prothrombotic endothelial cell phenotype | |

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| | induced by cocaine and plasma from cocaine consumers PMID: 25234816 | |
| 40 | The antitumor activity of LCL-SIM (liposomal simvastatin) depends on the presence of functional tumor-associated macrophages (TAM) in tumor tissue and is mainly based on the reduction of the TAM-mediated oxidative stress. PMID: 25444912 | |
| 41 | Protective effect on cardiovascular disease through the inhibition of SIRT1 expression in coronary artery disease patients. PMID: 25582759 | |
| 42 | Statin decreases the oxidative stress caused by noise exposure PMID: 25599753 | |
| 43 | Simvastatin and rosuvastatin significantly ameliorate experimental colitis in rats PMID: 25821305 | |
| 44 | Antioxidant activity of statins appear to be the main mechanisms involved in reducing the frequency of mutant spots and consequent modulation of the damage induced by Doxorubicin. PMID: 25846503 | |
| 45 | Simvastatin clearly lowers the serum levels of CRP and IL-6, and the white blood cell count in dialysis patients. PMID: 25866715 | |
| 46 | Anti epilepsy PMID: 25901524 | |
| 47 | Neuroprotective PMID: 25912435 | |
| 48 | Anti Osteoarthritis PMID: 25933963 | |
| 49 | Anti perioperative myocardial damage PMID: 25968407 | |
| 50 | Regulates Coenzyme Q10 a naturally-occurring coenzyme with antioxidant effects | |
| 51 | Against antioxidant/antiinflammatory properties of HDLs in hypercholesterolemics PMID: 26084126 | |
| 52 | Anti-inflammatory; Antioxidant; against Biphosphonate; Gastric damage PMID: 26403426 | |
| 53 | Antioxidant; Arylesterase; Cardiovascular disease; PMID: 26416579 | |
| 54 | Ameliorative effect of statin therapy on oxidative damage in heart tissue | |

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| | PMID: 26456720 | |
| 55 | Simvastatin inhibits oxidative stress via the activation of nuclear factor erythroid 2-related factor 2 signaling in trophoblast cells. PMID: 26556031 | |
| 56 | Fluvastatin Decreases Oxidative Stress in Kidney Transplant Patients PMID: 26707305 | |
| 57 | Antioxidation Effect of Simvastatin in Aorta and Hippocampus PMID: 26798426 | |
| 58 | modulating effect of simvastatin was also observed on DNA damage induced by DXR (doxorubicin) PMID: 26829615 | |
| 59 | Antagonistic effect and mechanism of Rosuvastatin on myocardial apoptosis<br>PMID: 26849935 | |
| 60 | non-cholesterol-lowering actions (anti-inflammatory, antioxidant and antithrombotic)<br>PMID:26930419 | |
| 61 | antioxidative properties of atorvastatin through down-regulating NOX1<br>PMID: 26957227 | |
| 62 | atorvastatin and artichoke leaf tincture reduce oxidative stress<br>PMID: 27071286 | |
| 63 | Antioxidant activity of simvastatin prevents ifosfamide-induced nephrotoxicity.<br>PMID: 27087071 | |
| 64 | simvastatin-conferred protection of eNOS (endothelial nitric oxide synthase) activation, NO production, and angiogenesis as well as the clinical outcome of cardiovascular events.<br>PMID: 27091343 | |
| 65 | effect of each statin on the antioxidant and cytoprotective enzyme, heme-oxygenase 1. PMID: 27207105 | |
| 66 | Statin use decreased the IL-1β and MPO levels PMID: 27290718 | |
| 67 | Simvastatin induces the activation and nuclear translocation of Nrf2 and the expression of various anti-oxidant enzymes via ERK and PI3K/Akt | |

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| | pathway PMID: 27323826 | |
| 68 | protective effects of simvastatin against alendronate-induced gastric ulceration. PMID: 26403426 | |
| 69 | Simvastatin protects human osteosarcoma cells (MG63)from oxidative stress-induced apoptosis through mitochondrial-mediated signaling. PMID: 22012179 | |
| 70 | Simvastatin prevents ifosfamide-induced nephrotoxicity. PMID: 27087071 | |
| 71 | effects of statins are anti-inflammatory, anti-proliferative, antioxidant. PMID: 27146293 | |
| 72 | Simvastatin-induced anti-oxidant enzymes. PMID: 27323826 | |
| 73 | Treatment with the cholesterol-lowering drug lovastatin reduced cell death by inhibiting the production of reactive oxygen species, but did not prevent lysosomal cholesterol increase. PMID: 28109635 | |
| 74 | Pravastatin (PS) does not cause ROS and cell death but also induces autophagy. PMID: 28004006 | |
| 75 | Atorvastatin reduced ROS. PMID: 27649495 | |
| 76 | Atorvastatin and rosuvastatin have similar effects on oxidative status in patients with acute myocardial infarction PMID: 28429691 | |
| 77 | Antioxidative potentials of atorvastatin and simvastatin during the different degrees of hyperhomocysteinemia (HHcy) in rats PMID: 28620818 | |

| B | Bisphosphonates | |
|---|---|---|
| | **Bisphosphonates Pro Antiox** | **Bisphosphonates Contra Antiox = Pro ROS** |
| 1 | Human endothelial cells PMID: 16440584 | Prostate cancer and multiple myeloma<br>Pro-oxidant synergism of Panbinostat (HDACi) and Bisphosphonate<br>PMID: 24157872 |
| 2 | Human endothelial cells PMID: 16216433 | Fibrosarcoma PMID: 23242142 |
| 3 | Cells (hematopoietic and musculuskeletal) infected with Paramyxovirus in Paget's disease PMID: 10321921 | Human erythrocytes PMID: 21843812 |
| 4 | Bisphosphonates alleviated oxidative stress induced by cancer.<br>PMID: 24308847 | Lung cancer PMID: 23045963 |
| 5 | Alendronate anti ROS in osteoblasts (2014, Lezcano V et al)<br>PMID: 24698731 | ZA may aggravate renal injury during I/R by increasing cytokine production and apoptosis. PMID: 25746831 |
| 6 | reducing nitric oxide synthase expression<br>PMID: 24831353 | Bisphosphonate-related osteonecrosis of the jaw PMID: 26026888 |
| 7 | increased oxidative stress induced by periodontal infection in rats can be ameliorated by bone-targeted antiresorptives. PMID: 25101489 | Alendronate-induced gastric ulceration. PMID: 26403426 |
| 8 | 3-keto-1,5-bisphosphonates 1 could be considered as safe antioxidant agents PMID: 25483977 | Use of Zoledronic Acid Augments Ursolic Acid-Induced Apoptosis in Human Osteosarcoma Cells through Enhanced Oxidative Stress and Autophagy.<br>PMID: 27916903 |
| 9 | Ibandronate exerted cellular antioxidant effects through the vasoprotective effects on the impaired endothelium<br>PMID: 27035426 | |
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