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EDITORIAL

In focus in HCB

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In this last Editorial for volume 152 (as well as for 2019), we are pleased to once again highlight three Original Papers. We would also like to introduce a new year end feature, a listing of the "Most popular articles published in HCB 2 years ago" (that is, published in 2017). Two years seemed like a good choice for ascertaining the immediate influence of a published manuscript. We hope you enjoy perusing the Table of "Most Popular Manuscripts", the overviews of the three highlighted articles, as well as the further contents of this last issue of HCB for 2019. Finally, on behalf of the entire Editorial Board, we offer you our best wishes for good health and scientific prosperity in the New Year!

Most popular articles published in HCB in 2017

We exploit the publication of the last issue of HCB in 2019 to look back to volumes 147 and 148 of 2017 and ascertain how the scientific community appreciated the published manuscripts during the following 2 years. As previously presented in the Editorial from July (Taatjes et al. 2019), the number of pdf downloads was the criterion used to assess the overall impact of a scientific article. Notably, 27% of the published articles fell into the category ≥ 1000 times downloaded (Table 1), while 43% were downloaded between 500 and 999 times. A main conclusion from Table 1 is that the articles published in HCB are highly representative of the multifaceted field of modern histochemistry, immunohistochemistry, and in situ molecular techniques and their manifold applications in basic and applied research. For instance, this includes the three topmost downloaded papers, "An introduction to the sugar code" by Gabius and Roth (2017) and reviews on eukaryotic protein glycosylation by Corfield (2017) and sialylation of *N*-glycans by Bhide and Colley (2017). Other authors reported about peroxisomal abnormalities in the human IHH hepatocyte cell line (Klouwer et al. 2017) and rotenone effects on peroxisomal dynamics (Passmore et al. 2017), or glioma cell invasion along blood vessels and in astrocyte-rich stroma (Gritsenko et al. 2017), invasion of both uterine arteries and veins by extravillous trophoblasts (Moser et al. 2017), and the application of in situ padlock probes to analyze heterogenity in colorectal cancer (El-Heliebi et al. 2017). Volume–SEM combined with stereology was used to quantify the Golgi apparatus structure (Ferguson et al. 2017). Finally, qualitative and quantitative methodical studies and their application, for instance, included combined orcein and martius scarlet blue (OMSB) staining for the analyses of atherosclerotic plaques (Gajda et al. 2017), a laser capture microdissection protocol for gene expression analysis in the brain (Garrido-Gil et al. 2017) and a review on lectin histochemistry (Manning et al. 2017).

Alterations in placental ROS-associated components with obesity

Placental vascular dysfunction can lead to a variety of pathological pregnancy conditions; therefore, maintaining an adequate placental blood supply is of paramount importance for fetal health and development. Blood vessel growth is determined by a number of factors, including the presence of vascular endothelial growth factor (VEGF) together with nitric oxide (NO), which moderates vascular tone. NO production itself is regulated by the presence of cell-specific nitric oxide synthases (NOS), including inducible (iNOS) and endothelial (eNOS). In high concentrations, NO can combine with superoxide to yield the reactive compound peroxynitrite, which when combined with proteins results in the production of nitrotyrosine, a member of the detrimental

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Table 1 Most popular articles published in HCB in 2017

*n**	Article
5200	Gabius and Roth: An introduction to the sugar code. (Gabius and Roth 2017)
3300	Corfield: Eukaryotic protein glycosylation: a primer for histochemists and cell biologists. (Corfield 2017)
3000	Bhide and Colley: Sialylation of *N*-glycans: mechanism, cellular compartmentalization and function. (Bhide and Colley 2017)
2400	Mayer et al.: C-type lectins: their network and roles in pathogen recognition and immunity. (Mayer et al. 2017)
1900	Gritsenko et al.: Recapitulating in vivo-like plasticity of glioma cell invasion along blood vessels and in astrocyte-rich stroma. (Gritsenko et al. 2017)
1700	Hlavaty et al.: Tropism, intracerebral distribution, and transduction efficiency of HIV- and SIV-based lentiviral vectors after injection into the mouse brain: a qualitative and quantitative in vivo study. (Hlavaty et al. 2017)
1700	Prokesch et al.: Placental DAPK1 and autophagy marker LC3B-II are dysregulated by TNF-alpha in a gestational age-dependent manner. (Prokesch et al. 2017)
1600	Roth and Zuber: Quality control of glycoprotein folding and ERAD: the role of *N*-glycan handling, EDEM1 and OS-9. (Roth and Zuber 2017)
1500	El-Heliebi et al.: Visualization of tumor heterogeneity by in situ padlock probe technology in colorectal cancer. (El-Heliebi et al. 2017)
1500	Ferguson et al.: Quantifying Golgi structure using EM: combining volume–SEM and stereology for higher throughput. (Ferguson et al. 2017)
1500	Gajda et al.: Combined orcein and martius scarlet blue (OMSB) staining for qualitative and quantitative analyses of atherosclerotic plaques in brachiocephalic arteries in apoE/LDLR (−/−) mice. (Gajda et al. 2017)
1500	Moser et al.: Extravillus trophoblasts invade more than uterine arteries: evidence for the invasion of uterine veins. (Moser et al. 2017)
1500	Nürnberger et al.: Giant crystals inside mitochondria of equine chondrocytes. (Nürnberger et al. 2017)
1500	Qui et al.: Hair follicle stem cell proliferation, Akt and Wnt signaling activation in TPA-induced hair regeneration. (Qui et al. 2017)
1400	Ranftler et al.: Golgi apparatus dis- and reorganizations studied with the aid of 2-deoxy-D-glucose and visualized by 3D-electron tomography. (Ranftler et al. 2017)
1300	Nielsen et al.: Identification of markers for quiescent pancreatic stellate cells in the normal human pancreas. (Nielsen et al. 2017)
1300	Kopitz: Lipid glycosylation: a primer for histochemists and cell biologists. (Kopitz 2017)
1300	Manning et al.: Lectins: a primer for histochemists and cell biologists. (Manning et al. 2017)
1200	Devriese et al.: T84 monolayers are superior to Caco-2 as a model system of colonocytes. (Devriese et al. 2017)
1200	Gostomska-Pampuch et al.: Protective effects of levamisole, acetylsalicylic acid, and alpha-tocopherol against dioxin toxicity measured as the expression of AhR and COX-2 in a chicken embryo model. (Gostomska-Pampuch et al. 2017)
1200	Passmore et al.: The respiratory chain inhibitor rotenone affects peroxisomal dynamics via its microtubule-destabilising activity. (Passmore et al. 2017)
1200	Zakrewski et al.: Expression and localization of myosin VI in developing mouse spermatids. (Zakrewski et al. 2017)
1100	Bando et al.: Retinoic acid regulates cell-shape and -death of E-FABP (FABP5)-immunoreactive septoclasts in the growth plate cartilage of mice. (Bando et al. 2017)
1100	Garrido-Gil et al.: Laser capture microdissection protocol for gene expression analysis in the brain. (Garrido-Gil et al. 2017)
1100	Kaltner et al.: Galectins: their network and roles in immunity/tumor growth control. (Kaltner et al. 2017)
1100	Klouwer et al.: Peroxisomal abnormalities in the immortalized human hepatocyte (IHH) cell line. (Klouwer et al. 2017)
1100	Milani et al.: VASA expression suggests shared germ line dynamics in bivalve molluscs. (Milani et al. 2017)
1000	Hanukoglu et al.: Expression of epithelial sodium channel (ENaC) and CFTR in the human epidermis and epidermal appendages. (Hanukoglu et al. 2017)

*Threshold number of pdf downloads ≥ 1000 as per November 2019

reactive oxygen species (ROS). Since elevated ROS are common in inflammatory conditions such as obesity, elevated NO levels in umbilical cord blood from newborns of obese mothers have recently been reported (Gallardo et al. 2015). Salvolini and colleagues (2019) sought to investigate the expression of VEGF, eNOS, iNOS, nitrotyrosine, and NO in placental tissue from normal weight control and obese mothers. Placental samples were rapidly frozen and subsequently used for immunohistochemistry, real-time quantitative PCR (Q-PCR), and measurement of tissue NO levels. Immunohistochemical analysis was performed for iNOS, eNOS, nitrotyrosine, and VEGF in both placental synctiotrophoblasts (SCs) and endothelial cells (ECs). Semi-quantitative analysis revealed the following results: (1) iNOS expression was similar in both cell types from placentas from both normal weight and obese women; (2) eNOS showed more expression in ECs from obese compared to control samples; (3) both VEGF and nitrotyrosine were not observed in SCs from the controls, with modest amounts of staining found in the obese group; and (4) placental

expression of both VEGF and nitrotyrosine was elevated in ECs from obese group compared to the control group. Q-PCR data showed elevated expression of both VEGF and eNOS genes in placentas from obese women compared to the control group, while iNOS expression was similar for both groups. Finally, NO levels were found to be elevated in placental tissue from obese women compared to those from normal weight controls. These results suggest that the upregulation of expression of placental VEGF and eNOS in endothelial cells, with concomitant increased NO may lead to placental villous vasodilation to compensate for reduced blood flow accompanying obesity.

FoxN1 impacts on thymic cortex-medulla differentiation

The cortex and medulla of the thymus are composed of two phenotypically different thymic epithelial cell (TEC) types. The cortical TECs are important during early steps of T-cell development, whereas medullary TEC are crucial for the generation of central tolerance to self-reactive T-cell clones (Kondo et al. 2017). It has been shown that FoxN1 is a key transcription factor for TEC differentiation and important for the expression of various TEC genes (Vaidya et al. 2016; Zuklys et al. 2016). In their previous work, Munoz and colleagues (2015; Munoz and Zapata 2018) have shown that early thymic organogenesis and cortex–medulla differentiation share similarities with the first steps of a process of branching morphogenesis and lumen formation. In the present work, Munoz et al. (2019) have tested their hypothesis that the specific differentiation program of the WT thymus would imply a primogenial pattern of branching morphogenesis present in the nude thymus that is modified by FoxN1 expression and the arrival of lymphoid precursors. For this, they performed a comparative analysis of thymus organogenesis in nude (FoxN1−/−) mice, alymphoid thymi of NOD SCID gamma mice, that express FoxN1, and Ikaros null/null (Ikaros−/−) mice by applying double immunofluorescence and 3D reconstruction. Based on the highly detailed analysis, the authors concluded that "FoxN1 expression in the thymic primordium inhibits a basic morphogenetic pattern of tubulogenesis and induces the expression of genes that drive TEC differentiation at different levels. The combination of both results in a thymic-specific development that induces a nonpolarized epithelium necessary for thymocyte—TEC interactions and specification of two major TEC subsets, cTECs and mTECs".

Association between adipocytes and mast cells in superficial fascia

Fascia, the supporting elastic material separating organs and tissues is found throughout the body, from just below the dermis to visceral organs themselves, and can be categorized according to anatomic location as (1) superficial, (2) deep, (3) skeletal muscle-associated, and (4) visceral organ-associated. Rather than serving as just an inert, supporting structure, tissue fascia possesses complex cellular networks. In the rat, for instance, the number of cells, such as adipocytes in the superficial fascia increases with growth (Su et al. 2016). These same authors (Su et al. 2016) also found that the superficial fascia was home to abundant preadipocytes, capable of differentiating into mature adipocytes and creating a thin adipose layer. This group has now extended these observations to analyze the possible interactions between superficial fascia preadipocytes and mast cells, with the premise that mast cell secretions may aid in preadipocyte-to-adipocyte maturation (Zhang et al. 2019). They performed a series of complex morphometric analyses into the regional association of adipocytes and mast cells in histochemically stained whole mount sections from rat superficial fascia obtained from animals of 4 and 8 weeks of age. Stained whole mount sections were scanned with a whole slide imager, followed by a series of morphometric analyses performed with ImageJ. Measured and analyzed parameters were selected to reveal spatial associations between objects (cells), and included fascia area together with cell count, spatial pattern analysis assessed by variance–mean ratio (V/M; Armstrong 2006) and Morisita index of dispersion (Morisita 1959), and the degree of chosen feature spatial association by morphometry coefficient. The results from these comprehensive analyses revealed that indeed, mast cells frequently appeared in superficial fascia regions populated with adipocytes and that this phenomenon increased during post-natal growth. Moreover, it was found that mast cells and adipocytes were spatially aggregated in clusters, with distributions positively correlated with each other, as well as correlated with the overall size of the adipocytes and the formation of primitive adipose lobule areas. These extensive morphometric results should form the basis for further investigations into the physiological interactions between superficial fascia adipocytes and mast cells.

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