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CHARITÉ Comprehensive Cancer Center Universitätstumorzentrum

PUBLIC KEYNOTE LECTURES

within the

14th Japanese-German Cancer Workshop

Fuyuki Ishikawa

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Telomere, Aging and Cancer

Petra Boukamp

German Cancer Research Center (DKFZ), Genetics of Skin Carcinogenesis

The microenvironment: a determinant for normal and tumor growth of human skin keratinocytes

Chair: M. Oshima, R. Schäfer

Friday, November 14, 2014, 4 pm - 6 pm

Kaiserin Friedrich-Haus, Robert-Koch-Platz 7, Lecture Hall

Further information: http://cccc.charite.de/aktuelles/veranstaltungskalender

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dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

50 Jahre – Forschen für ein Leben ohne Krebs

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Fuyuki Ishikawa: Telomere, Aging and Cancer

Abstract:

The end of linear DNAs present in eukaryotic nuclei is called telomeres. Telomeres are chromatin consisting of telomere DNA and associated proteins. The conventional DNA polymerases do not completely replicate telomere DNAs, leaving shortened daughter telomere DNAs (end replication problem). Progressive telomere shortening during repeated rounds of cell growth has been attributed to growth-arrested state found with normal cells that have experienced excessive growth (replicative senescence). Telomerase is active in germ cells, some somatic cells and most cancer cells, thereby compensating the telomere reduction and enabling cells proliferate extensively.

We have studied molecular mechanisms of telomere functions using fission yeast, Xenopus egg extracts and mammalian cells. We have shown that the chromatin structure at telomeres is highly conserved between fission yeast and higher eukaryotes. This indicates that fission yeast serves as a good model system to understand human telomeres.

We demonstrated that the DNA checkpoint sensor kinases, ATM and ATR, are required for telomere maintenance in fission yeast. This finding was enigmatic on the surface: Telomeres are supposed to protect DNA ends from being recognized by DNA damage checkpoint. However, we found that ATM and ATR are indeed required for telomerase recruitment to telomere DNA, leading telomere elongation counteracting to the end replication problem.

Telomeres are unique in its way of the conventional DNA replication. We have identified a novel ssDNA-binding protein complex called CST (for Ctc1-Stn1-Ten1). We will discuss about the biological function of this new member of telomere proteins.

Petra Boukamp: The microenvironment - a determinant for normal and tumor growth of human skin keratinocytes

Abstract:

Regulation of human normal epidermis including stem cell maintenance, aging, as well as carcinoma cell invasion is highly dependent on an interaction with and the quality of its environment. To study normal stem cell maintenance and tumor-host interaction we have established model systems allowing for the adequate 3D organization and relevant interaction of the epidermis with its microenvironment, the dermal stroma. While in early studies with collagen-based organotypic cultures (OTCs) the epithelium only remained vital for 3 to 4 weeks it was suggested that such models promote stem cell differentiation rather than maintenance. However, preventing collagen degradation disproved this hypothesis. Improving the stability of the dermal equivalent and allowing for the formation of an authentic dermal matrix, such dermal equivalents now support stem cell maintenance and promote homeostatic epidermal regeneration for >6 months, allow for physiological stem cell activation/mobilization during e.g. epidermal regeneration upon wounding as well as upon rejuvenation of the skin upon skin peeling.

This is regulated by an intense double paracrine interaction that goes far beyond the double paracrine loop described previously. Factors, so far predominantly viewed in their role as immune-stimulants are expressed and by blocking experiments we are now able to assign them to specific functions in epidermal growth and/or endothelial morphogenesis. Even more so, we identified the dermal fibroblasts as the target cells of photoaging causing the formation of a chondrocyte-type matrix. This in turn provided a restrictive niche by hindering epidermal long-term regeneration. Blocking the regulatory cue involved in this fibroblast transdifferentiation restored epidermal stem cell function suggesting for and admitting of a still adjustable modulation also in aging skin.

Tumor cell invasion is similarly based on an intense tumor-stroma interaction and ECM stiffness is supposed to pave the way for tumor cells, thus highlighting the tumor microenvironment as an essential ingredient of cancer malignancy. We now show that Wnt-activated human fibroblasts promote human keratinocyte proliferation and matrix destruction and provide evidence for such a scenario in defined sites of human cutaneous squamous cell carcinomas (SCC). To further unravel the contribution of this tumor-stroma interaction, we established a human 3D tumor-invasion model which we now use to unravel molecular cues in the interaction of tumor cell and fibroblasts in order to support or even suppress tumor cell invasion.