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Editorial

Rare cancers: What we can learn from them

We are proud to introduce the new *IJBCB* Directed Issue on Rare Cancers which highlights the current state-of-the-art molecular diagnostics and etiopathology of rare cancers. We are particularly grateful to our Guest Editors Professor Janusz Limon (Medical University of Gdansk, Poland), Professor Markku Miettinen (National Cancer Institute, Bethesda, USA) and Dr. Jerzy Lasota (National Cancer Institute, Bethesda, USA) who compiled an excellent collection of reviews and original research papers on various types of rare cancers. We very much hope that this issue will provide a great reference for the most recent advances in revealing the often complex molecular basis of various rare cancer types, and translating this knowledge into targetted clinical therapies.

Typically common cancers occur in organs and tissues with rapid cell proliferation, such as the gut or skin. There is no clear definition for rare cancers, but generally cancers are considered rare when (1) they originate from an unusual tissue, (2) they originate from an unusual cell type that needs a highly specialized treatment, (3) they form an uncommon or a rare subtype of a common cancer. The frequency of rare cancers is estimated differently in various countries and ranges from 1 to 15 cases per 100 000 population per year.

All cancers might be divided into three classes (Benz et al., 2007). The first class comprises cancers linked to age, with strongly rising incidence in the elderly population. The underlying mechanism is widely accepted to be related to exposure to environmental stress, which leads to the accumulation of cellular damage with age, thus such cancers are typically found in rapidly dividing tissues (e.g., lung and colon). The second group is the childhood cancers. These are often linked to aberrant development of stem cell and/or progenitor cell deregulation. The third group consists of cancers that are linked to hereditary mutations in cancer predisposition genes, such as BRCA1 and BRCA2. With the novel knowledge acquired from the genomics of rare cancers, we might classify these as the fourth group.

One might expect that the cancers linked to hereditary predisposition might lead us to discover the causes of cancer. However, our knowledge has not advanced as much as we would have hoped. Typically predisposition genes are tumor suppressors and their reduced function eventually permits malignant transformation, hence they are not typically identified as drivers of tumor progression and metastasis (Haber and Settleman, 2007).

Rare cancers often arise, as their name indicates, from a specific cell type in an organ or tissue, e.g., from the insulin producing cells of the pancreas for *islet cell carcinoma*, or the sperm cell support cells of the testis for *sertoli cell carcinoma* (Visvader, 2011). Many rare cancers are childhood cancers, such as the *neuroblastoma*, and their cause is unknown. But there are also some adult cancers, such as mesothelioma, for which the cause is clearly linked to asbestos exposure.

Thus, rare cancers are unusual, as they occur in a tissue that typically is not highly proliferative and does not typically generate tumors, and/or they occur at an unusually young age. But, as our mechanistic knowledge of tumorigenesis progresses, we discover that rare cancers are often linked to one major driving factor, which is not the case for the majority of common tumors. There is hope that efficient treatment targets will be identified for specific rare cancers once these drivers and their molecular pathways are known.

One example of such a tumorigenesis driver is the defective and constitutive activation of a protein kinase at an ectopic cellular location in mesenchymal tumors (Płaszczyca et al., 2014; see this issue). The rapid progress on RNA and genome sequencing data allowed us to identify many other drivers of rare cancers. Often these are gene fusions in the cancer cells, generating protein chimeras with novel dominant negative functions. Such examples are found in the *round cell sarcoma*, or *Ewing sarcoma*, in which the Ewing sarcoma protein is fused to the transcription factor FLT1. This Directed Issue is a collection of articles that give us a glimpse on the progress made in the field. There is hope that with the rapid progress in various 'omics' the drivers of particular rare cancers can be identified and precise medical treatments can be applied to these rare and often terminal diseases.

Finally we would like to thank all the contributors to this issue and those researchers who have devoted their lives to exploring cancers that because of their rareness are underexplored. But of course to the sufferers and their family and friends the occurrence of the rare cancer is a catastrophic event, and they look to scientist and the broader medical community for cures. Finding these cures and improving care requires long term commitments from all those involved, as well as the funding bodies and pharmaceutical industry without whom little can be achieved.

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